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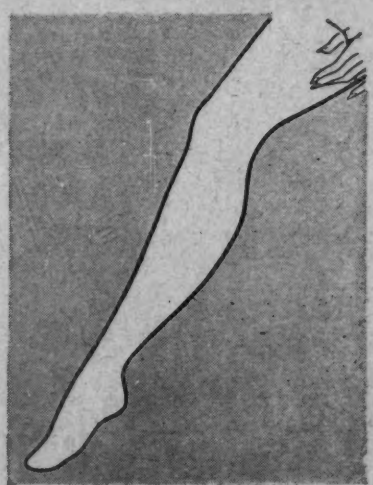

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BRITISH MEDICAL JOURNAL

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POST-MYOCARDIAL-INFARCTION SYNDROME

BY

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The post-myocardial-infarction syndrome is characterized by prolonged pericardial friction, persistent chest pain, continuing fever, and, in many instances, by pericardial and pleural effusion. These features develop during the first few weeks after myocardial infarction. The whole illness may pursue a relapsing course for months.

The syndrome was first described by Dressler (1956), and in 1959 he reported its occurrence in 44 patients. He estimated that the syndrome complicates from 3 to 4% of cases of myocardial infarction, and it is therefore remarkable that it has escaped recognition until recent years. Weiser, Kantor, and Russell (1959) have described four similar cases, but, so far as we are aware, no series has been reported in the British literature. Two of the five cases described in this paper were seen early in 1960, and within six months two others were diagnosed. The remaining one was identified from a review of patients classified as having pericarditis complicating myocardial infarction; in this patient, the significance of the pericarditis and other features of the syndrome had not been appreciated at the time. A review of 500 consecutive patients admitted to the Edinburgh Royal Infirmary on account of acute myocardial infarction revealed only three who developed the features of the post-myocardial-infarction syndrome—an incidence of less than 1%.

Case 1

A man aged 53 had increasing effort angina for two weeks. An acute myocardial infarct, with classical and severe precordial pain lasting for two hours, occurred immediately before admission. There was no history of previous vascular or other disease. On arrival in hospital he was shocked, with a blood-pressure of 100/80. With morphine, oxygen, and the relief of pain, the clinical features of shock disappeared but hypotension remained; on the fourth day after admission his blood-pressure fell to 80/50 and was subsequently in the region of 115/70. The first electrocardiogram taken on the morning of admission showed an acute transmural posterior myocardial infarct with widespread myocardial ischaemia, and a further record taken later on the same day showed the development of atrial fibrillation with a ventricular rate of approximately 120 a minute; on the next day sinus rhythm returned with a prolonged P–R interval at 0.26 second. Subsequent electrocardiograms continued to show transmural posterior myocardial infarction with the expected changes of healing.

During the first two days after admission he experienced several transient episodes of precordial pain suggestive of myocardial ischaemia, but subsequently this pain became dull and intermittent, and was mostly associated with inspiration. This different type of pain continued from the first to the twenty-fourth day. From the third to the tenth day coarse pericardial friction could be heard in systole and diastole. During the first four days the expected febrile response to myocardial infarction occurred, but subsequently a pyrexia continued for the next eight weeks (Fig. 1). The E.S.R. rose from 10 mm./hour to 102 mm./hour seven days after admission, and remained between 56 and 110 mm./hour for the next nine weeks (Fig. 1). On admission the haemoglobin level was 90%, at the beginning of the second week it was 80%, and at the beginning of the fifth week it was 65%. During the third week the heart sounds became progressively softer, and on the 22nd day a pericardial effusion was suspected clinically and confirmed radiologically (Fig. 2).

During the third week it was suspected that the patient might have the post-myocardial-infarction syndrome, and 15 mg. of prednisolone was given daily. This was continued for 19 days and then stopped, since it seemed that the pyrexia, the elevation of the E.S.R., and the pericardial effusion were not responding. From the second day of admission 1 mg. of digoxin was given orally every day for 30 days, and when the pericardial effusion was recognized 2 ml. of mersalyl was given on four occasions. After the withdrawal of prednisolone the pyrexia returned until a daily dose of 15 mg. of prednisolone was given once more (Fig. 1); this was continued for 30 days. During this period the pyrexia decreased, the E.S.R. fell from the region of 100 mm./hour to 21 mm./hour, the pericardial effusion gradually began to decrease, and the tendency to develop congestive failure no longer occurred.

Phenindione was administered orally throughout this period, and has been continued on a long-term out-patient basis. After his discharge from hospital this man made good progress, and returned to his work as a caretaker seven months after the myocardial infarct. All radiological evidence of the pericardial effusion had disappeared 14 weeks after its recognition.

Case 2

A man aged 56 had an occasional sharp pain in the right side of his anterior chest, partly in relation to exertion, for four weeks. An acute myocardial infarct, with severe but sharp pain deep to the sternum, marked breathlessness, sweating, paraesthesiae in the hands, and vomiting, occurred during the day before his admission to hospital. The pain occurred intermittently in severe form for 24 hours. There was no history of previous vascular or other disease. On admission he had orthopnoea, cyanosis, and engorgement of the neck veins. There was no tachycardia. Bilateral basal crepitations were heard, but there was no oedema. He was not shocked; his blood-pressure was 160/110; it fell to the region of 116/80 and remained at this level throughout the rest of his five-weeks stay in hospital. The first electrocardiogram indicated a recent transmural anterior myocardial infarct and probably also a recent transmural posterior myocardial infarct. Subsequent electrocardiograms confirmed that transmural myocardial infarction had occurred in both the anterior and the posterior walls of the left ventricle. No arrhythmia or conduction defects occurred. Only one estimation of the serum glutamic oxalo-acetic transaminase (S.G.O.T.) level was recorded; this was obtained 24 hours after the myocardial infarct and was elevated at 97 units.

The expected febrile response to myocardial infarction developed and subsequently settled, but at the beginning of the third week a pyrexia in the region of 101° F. (38.3° C.) occurred for four days. At that time, pericardial friction was heard; it remained throughout his stay in hospital and persisted for three months after his discharge. It was not associated with pain, although for some weeks he complained of a vague sense of heaviness and discomfort in the chest. The E.S.R. rose from 2 mm./hour on the day of admission and remained at a level of 36 to 68 mm./hour

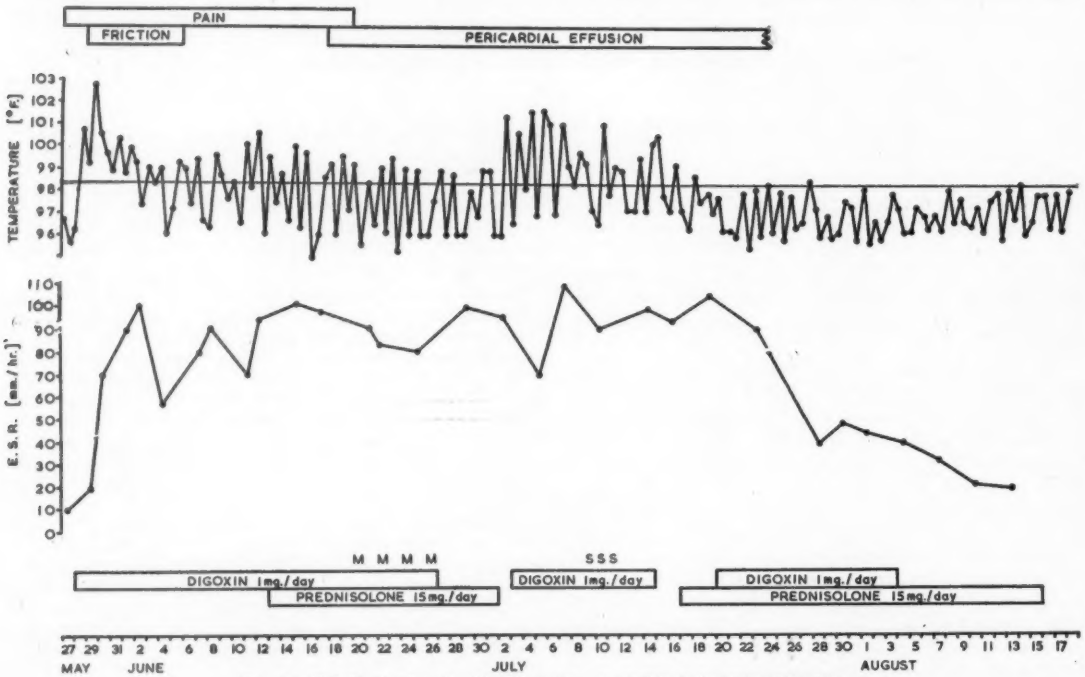
PAIN
FRICTION
PERICARDIAL EFFUSION
TEMPERATURE [°F.]
103 102 101 100 99 98 97 96
E.S.R. [mm./hr.]
110 100 90 80 70 60 50 40 30 20 10 0
M M M M
DIGOXIN 1mg./day
PREDNISOLONE 15mg./day
SSS
DIGOXIN 1mg./day
DIGOXIN 1mg./day
PREDNISOLONE 15mg./day
27 29 31 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 1 3 5 7 9 11 13 15 17
MAY
JUNE
JULY
AUGUST

FIG. 1.—Details of Case 1. M=Mersalyl. S="Saluric" (chlorothiazide).

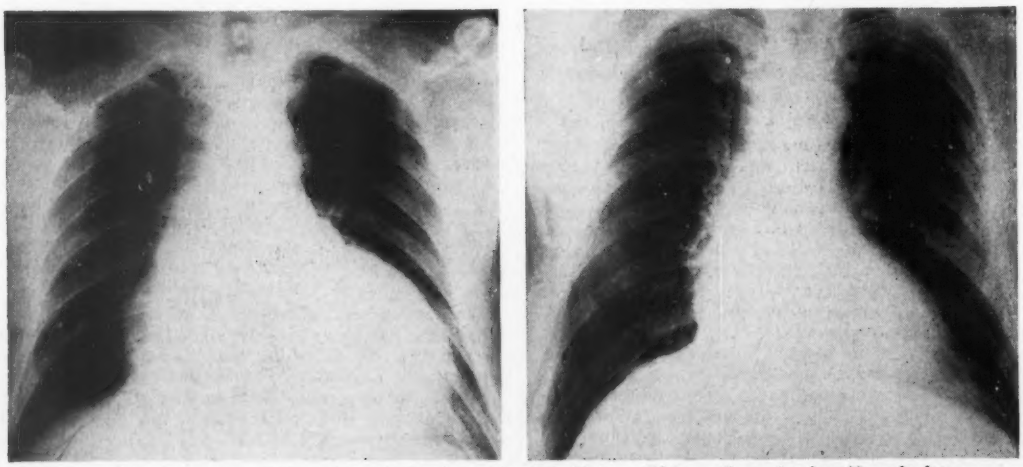

FIG. 2.—Case 1. Left, radiograph showing pericardial effusion. Right, radiograph taken 13 weeks later.

during the five-weeks stay in hospital; on discharge it was 46 mm./hour. At the time of the pyrexia at the beginning of the third week, there were radiological signs of patchy congestion at both bases associated with a transient right-sided pleural effusion. Slight generalized cardiac enlargement was observed radiologically during the fourth and fifth weeks, and it is possible that a small pericardial effusion may have developed.

Phenindione was administered throughout his stay in hospital, and continued on a long-term basis after his discharge. During the three years since his myocardial infarct he has remained reasonably well and has been able to return to his work as a crane-driver.

Case 3

A man aged 59 experienced effort angina for four days. An acute myocardial infarct, with very severe crushing chest pain for 15 minutes, occurred immediately before his admission to hospital. There was no history of previous vascular or other disease. On arrival in hospital he was in good condition and not shocked; blood-pressure 170/110 and subsequently 114/70. The first electrocardiogram indicated transmural anteroseptal myocardial infarction, which subsequently showed the expected signs of healing. The S.G.O.T. level reached 90 units 28 hours after the myocardial infarct.

On the second day a loud pericardial friction rub was heard, lasting for 16 days. At the same time he complained of a heavy pain made worse by inspiration. This discomfort continued intermittently during the next four or five days, but thereafter did not recur. A low-grade pyrexia and elevation of the E.S.R. persisted during his six weeks in hospital. On the fifth day after admission bronchial breath sounds were heard at the right base, where a moderately large pleural effusion subsequently developed. This persisted for two weeks and resolved spontaneously. Soon after he developed engorgement of the neck veins and sacral oedema, for which he was given bendrofluazide 7.5 mg. on eight occasions in association with 3 g. of potassium chloride daily. Phenindione was given only while he was in hospital.

When seen as an out-patient two months after the myocardial infarct a pericardial friction rub was again audible, particularly in diastole. His E.C.G. showed upward bowing of the ST segments in the standard and chest leads, indicating either some pericardial inflammatory reaction or continued ischaemia. On this occasion his E.S.R. was 41 mm./hour and radiologically there was some generalized cardiac enlargement, which may have been due to a small pericardial effusion. Screening examination showed diminished pulsation. During the five days prior to his out-patient visit, he had been aware of a dull pain in the left side of the lower part of the chest. This dull pain was aggravated by inspiration, and occasionally occurred over the front of the chest. It was not particularly severe, and was not associated with breathlessness, but remained for three weeks. During the next two months his E.S.R. remained elevated between 25 and 40 mm./hour, the ST elevation in the chest leads gradually decreased, and radiologically his cardiac enlargement disappeared.

Case 4

A man aged 78 had two attacks of anginal pain 10 days and four days before admission. An acute myocardial infarct with severe precordial pain lasting for four hours occurred on the day of admission. There was no history of previous vascular or other disease. On arrival in hospital he was pale and sweating, with a blood-pressure of 110/80. There was no evidence of cardiac failure. Within a few hours he ceased to complain of precordial pain, and his blood-pressure rose to 124/86. The first electrocardiogram taken on the day of admission showed an acute transmural posterior myocardial infarct with additional widespread myocardial ischaemia. Subsequent electrocardiograms showed the expected changes of healing with multiple supraventricular extrasystoles.

On the fourth day, coarse pericardial friction was heard both in systole and in diastole; this friction continued with only minor changes in character for 10 weeks. At no time during this period did the patient complain of precordial or pleuritic pain. Prior to the development of pericardial friction, there was a slight pyrexia which had almost settled but recurred with the friction and persisted (varying from 99 to 101° F.; 37.2 to 38.3° C.) for the same period as the friction. The E.S.R. was initially 48 mm./hour, and reached a maximum of 80 mm./hour during the eighth week of the illness. The haemoglobin level was 90% on admission, and subsequently fell to 80%. The white-cell count varied from 4,400 to 7,800/c.mm. The S.G.O.T. was not recorded. During the second week there was radiological evidence of pericardial effusion. Serial *x*-ray films during the subsequent 11 weeks showed some increase in this effusion followed by gradual resolution. At one stage there was evidence of inflammatory change in the right lower lobe with a small right basal effusion extending into the greater fissure. Despite the radiological appearances, there was no clinical evidence of an embarrassingly large pericardial effusion, and hence aspiration of the pericardial sac was not attempted. Furthermore, the pericardial friction was undiminished and the heart sounds remained loud.

On admission the usual treatment with phenindione was begun. During the fourth week numerous supraventricular extrasystoles were recorded, and quinidine sulphate was added to the regime. During the sixth week, because of radiological evidence of an inflammatory lesion in the right lower lobe, penicillin was given. By the seventh week it was clear that the patient had the post-myocardial-infarction syndrome, and it was therefore decided to give prednisolone 20 mg. daily. Unfortunately this appeared to precipitate mild congestive cardiac failure, and the pericarditis persisted; prednisolone was therefore stopped after seven days. Thereafter the failure was easily controlled with injections of mersalyl. During the ninth week phenindione was also stopped, on the grounds that it might be contributing to the post-myocardial-infarction syndrome.

After 12 weeks in hospital the patient was discharged in good health. All treatment had been stopped. He has since been seen on several occasions as an out-patient, and satisfactory progress has been maintained.

Case 5

A married woman aged 59, with a history of acute rheumatism in childhood and eclampsia during her only pregnancy, was admitted to hospital complaining of severe precordial pain which had been present for six hours. There was a moderate degree of shock with early signs of cardiac failure. An electrocardiogram showed transmural anterior myocardial infarction. The pain required morphine on the day of admission and pethidine on the following day, after which it did not recur. Treatment included rest, anticoagulants, diuretics, and a low-calorie diet as the patient was obese. Progress was uneventful apart from a small haemoptysis on the third day. There was a slight pyrexia during the first week in hospital. The E.S.R. was raised throughout the acute phase and was 83 mm./hour when the patient was discharged after five weeks in hospital.

Four weeks later she was readmitted with pain behind the lower sternum; it was burning in character, radiated to the right axilla, and was different from the pain of the original attack. Examination showed a pyrexia of 102° F. (38.9° C.) and signs of cardiac failure. On the day after admission a pericardial rub was heard. An electrocardiogram showed no sign of extension of infarction or of pericarditis. During the next two weeks the patient was extremely ill with a high fever uninfluenced by antibiotics. Repeated blood cultures were negative, the E.S.R. remained high (80 mm./hour), but the W.B.C. was not raised. During this time the right chest was aspirated and 200 ml. of blood-stained fluid was removed. The pericardial rub remained for three weeks. On the fifteenth day after admission the temperature fell to

normal, remained so for two weeks, then a low-grade pyrexia 98–100° F. (36.7–37.8° C.) continued for the next six weeks. On one occasion during this time a sharp attack of precordial pain occurred, depression of ST segment in the chest leads was seen, and anticoagulants were given for two weeks. Throughout her illness the blood-pressure varied from 120/70 to 150/95. Serial *x*-ray films from the time of admission showed the appearances of pericardial effusion and pleural effusions, which gradually improved during her stay in hospital.

At the beginning of the tenth week treatment with prednisolone 40 mg. daily was started. Temperature became normal and the patient remained afebrile until discharge three weeks later, when the dose had been reduced to 10 mg. daily. She continued to take 10 mg. of prednisolone as an out-patient. This was stopped six weeks after discharge, when *x*-ray examination showed a further decrease in heart size and disappearance of the pleural effusions. During the eight months since she left hospital the patient has kept well, apart from slight breathlessness on exertion.

Main Features of the Syndrome

The five patients described above presented with a clear diagnosis of myocardial infarction. In all of them the course of the illness was unusual and was characterized by features of the post-myocardial-infarction syndrome (see Table).

Pericardial Friction.—This is the clinical feature of greatest significance. Whereas the pericardial friction of myocardial infarction is early in onset and brief in duration, the friction of the syndrome usually occurs later and can hardly fail to attract attention by its extraordinary duration—120 days in Case 2 and 66 days in Case 4. In Case 3 friction persisted for only 16 days, but was heard again two months after the patient had been discharged from hospital. In Cases 1 and 5 the shorter duration—8 and 24 days respectively—may have been determined by the development of pericardial effusion.

Chest Pain.—The pain is variable in type, and the main feature is its difference in quality from the original infarction pain; it usually consists of a heavy dull discomfort confined to the anterior chest, and is often aggravated by inspiration. Furthermore, it arises when the pain of myocardial ischaemia has subsided or is subsiding. Dressler (1959) attributes it to the presence of pleuro-pericarditis, and stated that it is "absent only in exceptional cases." In our otherwise typical series chest pain was absent in one.

Pericardial Effusion.—In three of the five patients the *x*-ray appearances were typical of pericardial effusion; in the other two the appearances were only suggestive, but there was no other evidence of cardiac failure and both had prolonged pericardial friction. Dressler (1959) stated that he had observed intensely haemorrhagic pericardial exudate in the post-infarction syndrome, and adds that this may occur both with and without anticoagulant therapy. Nevertheless, the possibility of haemorrhagic cardiac tamponade in patients receiving anticoagulants in the presence of the syndrome must be considered by the physician, and in one of our patients anticoagulant therapy was stopped for this reason.

Pyrexia.—In this series irregular pyrexia persisted for periods up to 102 days, in contrast to the brief pyrexia of uncomplicated myocardial infarction. Prolonged pyrexia is therefore a striking component of the syndrome.

Erythrocyte Sedimentation Rate.—All five patients showed persistent and marked elevation of the E.S.R. during the active phase of the syndrome, which may last for many weeks.

Pleurisy.—Four of the patients developed small pleural effusions which were not preceded by detectable pleural friction. While pleurisy with or without effusion is a common feature of the syndrome, its diagnostic significance is limited, since the alternative causes of cardiac failure and pulmonary infarction are not easily excluded.

Pneumonitis.—Dressler (1959) reports that 10 of his 35 patients of whom adequate radiological study was made showed patchy or linear pulmonary infiltration which was commonly basal in situation; 3 of these 10 produced haemorrhagic sputum. Such features were not thought to be due to pulmonary infarction. Although the lungs of our patients showed minor radiological changes, we were reluctant to use the term "pneumonitis," which therefore does not appear in the Table. It is doubtful if this feature is specific enough to justify its inclusion in the syndrome.

Periostitis.—Roesler (1960) describes two cases with chest-wall pain after myocardial infarction. He attributes the pain to "periosteal involvement of chest-wall structures" and suggests that this might be added to the features of the post-myocardial-infarction syndrome. In other respects, however, his patients do not resemble the typical Dressler syndrome, being more akin to the "anterior chest wall syndrome" described by Prinzmetal and Massumi (1955). None of our patients had features of periostitis.

Discussion

Diagnosis.—The diagnosis of the post-myocardial-infarction syndrome should present little difficulty, provided that the physician is aware of its existence. The clinical features of prolonged pericardial friction with pyrexia and persistent elevation of the E.S.R. in a patient who has presented with obvious myocardial infarction form the basis of the diagnosis. Other and less constant features are non-ischaemic chest pain, pericardial effusion, and pleurisy with or without effusion. As Dressler (1959) points out, the clinical picture closely mimics the post-commissurotomy syndrome. Difficulty in diagnosis may occur when the clinical and electrocardiographic evidence of the original myocardial infarction is inconclusive; in these circumstances other causes of pericarditis and pyrexia, such as tuberculosis

Clinical Features of Five Patients with Post-myocardial-infarction Syndrome

Case No.	Sex and Age	Pericardial Friction (in Days)	Chest Pain or Discomfort (in Days)	Pericardial Effusion (in Days)	Pyrexia and Elevated E.S.R. (in Days)	Pleural Effusion (in Days)	Treatment	
							Anticoagulants	Steroids
1	M 53	3rd–10th	1st–24th	From 22nd	1st–63rd	None	Yes	On two occasions (relapse)
2	M 56	15th–135th	1st–42nd	Not definite	1st–24th	From 21st	,,	No
3	M 59	2nd–17th	1st–7th 51st–77th	,, ,,	1st–102nd	,, 5th	,,	,,
4	M 78	4th–70th	None	From 10th	1st–70th	,, 35th	,,	Yes
5	F 59	60th–84th	50th–80th	,, 60th	63rd–140th	,, 63rd	,,	,,

and systemic lupus erythematosus, would have to be considered. Recurrence of myocardial infarction and the onset of pulmonary infarction are other possible causes of confusion, but in our patients there was no difficulty in excluding these conditions. Congestive cardiac failure may reproduce two radiological features of the syndrome—namely, enlargement of the cardiac shadow and pleural effusion—but the syndrome should be suspected and diagnosed on the other more specific manifestations. The electrocardiogram is often unhelpful, since features of pericarditis may be overshadowed by those of extensive myocardial infarction; delay in disappearance of ST shifts was noted in three of our cases.

Aetiology.—The cause of the syndrome is unknown. Dressler (1959) argues that anticoagulant therapy, by causing leakage of blood into the serous cavities, might produce irritant pericarditis and pleuritis; but he notes that 11 patients in his series of 44 did not receive anticoagulants prior to the onset of the complication. Gery, Davies, and Ehrenfeld (1960) have found anti-heart antibodies in the serum of one patient suffering from the syndrome, thus supporting the suggestion of Dressler (1956) that it may be the result of an autoimmune reaction. Probably it should be regarded as a pericardial and pleural reaction to non-specific myocardial damage, and, as such, has the same aetiology as the post-commissurotomy syndrome.

Treatment.—In these days it is probable that most patients developing the syndrome will be receiving anticoagulant therapy. Even if it is agreed that anticoagulants do not cause the syndrome, the question of stopping them still arises because of the risk of precipitating haemorrhagic cardiac tamponade in the presence of pericarditis; Dressler (1959) reports a death from this cause, although it might be noted that the patient also had haemothorax, haemoperitoneum, and red blood cells in the urine, suggesting that there was an excessive bleeding tendency. The risk of precipitating haemorrhagic cardiac tamponade with anticoagulants must be weighed against the risk of recurrent infarction and thrombo-embolic complications without anticoagulants. If the autoimmune hypothesis of aetiology is correct it would clearly be desirable to give steroids. Three of our five patients received prednisolone; two showed a satisfactory response, but in the third prednisolone had to be stopped after seven days because of the onset of congestive cardiac failure. Dressler (1959) reported some success with prednisolone, although relapse was common when the drug was stopped; such a relapse occurred in one of our patients; this suggests suppression rather than elimination of the pathological process. Dressler (1959) also mentions that relief of pain with prednisolone is an important form of symptomatic treatment. As with anticoagulants, the benefit of steroid therapy is uncertain in the post-myocardial-infarction syndrome.

Prognosis.—All five patients eventually made a satisfactory recovery. Dressler (1959) also comments on the good prognosis. If the increased risk of cardiac tamponade is excluded the prognosis becomes that of the original myocardial infarction. The syndrome, however, prolongs the stay of the patient in hospital and increases discomfort during that time.

Summary

The clinical features are described of five patients who developed the post-myocardial-infarction syndrome. It closely resembles the post-commissurotomy syndrome, and is characterized by continued pericardial friction, prolonged pyrexia, persistently raised E.S.R., and chest pain of pleuro-pericardial type. Less constant features are pericardial effusion and pleurisy with or without effusion.

The post-myocardial-infarction syndrome probably complicates less than 1% of all cases of acute myocardial infarction. Although the prognosis is good, the patient's recovery is delayed for months.

Aetiology and the problems of treatment with anticoagulants and steroids are discussed.

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SEQUELAE OF URINARY INFECTION IN PREGNANCY

A FIVE-YEAR FOLLOW-UP

BY

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Infection of the urinary tract is relatively common during pregnancy and might be expected to lead, in some cases at least, to recurrent urinary infection or chronic pyelonephritis; it thus seemed worth while to review a number of patients five years after an attack of urinary infection during pregnancy to determine how many showed evidence of recurrent infection or chronic pyelonephritis at this time.

Material and Methods

Of 80 consecutive patients with definite evidence of urinary infection in pregnancy, diagnosed and treated in Queen Charlotte's Maternity Hospital at least five years previously, 50 were available for study. The other 30 either could not be traced (19) or were unwilling to come back to hospital for reassessment (11); no details of their present health or the number of deaths, if any, in the group are known. The investigations included: (1) full clinical examination, including blood-pressure readings, protein estimation, microscopy, and culture of the urine; (2) intravenous pyelography; and (3) a modification of the "pyrexal" test described by Pears and Houghton (1959). This was performed in 22 of the patients who had recurrent urinary infection or

showed radiological abnormalities at the follow-up examination. Blood-urea estimations were normal in all cases.

Urinary Infection During Pregnancy.—The infection was most common in the first pregnancy, but the onset of symptoms was more frequently seen in the third trimester than in the second. Most of the patients had clinical evidence of renal infection, more often on the right side than the left; half of them also had symptoms of an infection of the lower urinary tract. Five had no symptoms or signs apart from the urinary findings, but one of these subsequently underwent right nephrectomy for chronic pyelonephritis with hypertension. *Escherichia coli* was the organism found most frequently. Sulphonamides were used more often than any other drug, but eight patients were treated with potassium citrate only. The urine was not always examined after a course of treatment, and patients were sometimes discharged with active urinary infection.

Follow-up

Clinical Findings

The time of occurrence of urinary infections in the 50 patients up to the time of this follow-up examination is shown in Table I. Two had suffered urinary infections in childhood; one of these had undergone removal of an infected hydronephrotic kidney soon after the pregnancy, and the other was still suffering from recurrent attacks of urinary infection; this is in keeping with Woodruff and Everett's (1954) findings that urinary infections in pregnancy followed childhood infections only when these were recurrent or associated with lesions of the urinary tract.

Thirty-nine patients had experienced more than one attack; it would therefore seem that the urinary infection of pregnancy is usually only one episode in a recurrent disease. The first attack occurred before pregnancy in 19 and during pregnancy in 20; this suggests that pregnancy may have initiated the recurrent infection in one-half (20/39) of these cases. Only 11 patients gave a history of a single attack of urinary infection without recurrent or residual symptoms or signs.

While the blood-pressures were higher than would be expected for healthy women of a similar age-group, the significance of this finding is limited because of the small number in the series and of the differences in the method of recording the blood-pressure of the patients and controls.

The findings in catheter specimens of urine at the time of follow-up are shown in Table II. Because the urine was centrifuged before microscopy the presence of scanty leucocytes was ignored. Ten patients had definite urinary infection; only one of these had symptoms at the follow-up examination, but eight gave a history of attacks of recurrent urinary symptoms since the infection in pregnancy five years previously; the final catheter specimen of urine obtained after treatment of the infection at that time had shown leucocytes in three and leucocytes and positive bacterial culture in four of these patients, but no further treatment had been given. In five of the eight the history was suggestive of recurrent renal infection, and these probably have chronic pyelonephritis (Table IV, Cases 2, 3, 4, 6, and 10).

TABLE I.—*Time of Occurrence of Urinary Infection in 50 Patients*

Single attack during pregnancy		11
Recurrent attacks		39
Attacks began	In childhood	2
	Before pregnancy	17
	During ,,	20

TABLE II.—*Findings in Catheter Specimens of Urine at Follow-up of 50 Patients*

Normal		32
Abnormal		16
	Leucocytes + bacteria cultured	10
	Leucocytes	4
	Bacteria cultured	2
Catheter specimen of urine not obtained		2

Radiological Investigations

In 43 of the 50 cases "plain film" examination of the whole urinary tract was undertaken, followed by intravenous pyelography, routinely using 20 ml. of 45% sodium diatrizoate ("hypaque"). Seven patients were not examined—two because of a past history of allergy, and five because they failed to attend for the investigation. A careful assessment of the size of the kidneys was made and evidence of parenchymal contracture was especially sought.

Abnormal findings were noted in 19 of the 43 cases (Table III). A radiological diagnosis of chronic pyelonephritis was made in one patient because of overall contracture of the renal parenchyma with persistent irregularities in the margins of the minor calices, which were slightly dilated, especially in the mid-zone. She gave a history of recurrent infection of the upper urinary tract over the past six years; and urine examination at follow-up showed no bacteria and an increased leucocyte count which the injection of pyrexal did not increase.

TABLE III.—*Results of Intravenous Pyelography in 19 Abnormal Cases*

Chronic pyelonephritis with contracture of parenchyma and slight caliceal dilatation	1
Caliceal, pelvic, and ureteric dilatation	2
,, dilatation	4
Ureteric	2
Developmental anomaly of ureter	2
Ureterocele (unilateral)	1
Vesical diverticulum	1
Fundal identation of bladder	9
Total abnormalities	22

Fundal indentation of the bladder and dilatation of the upper renal tract occurred together in three patients.

When caliceal, pelvic, or ureteric dilatation was reported a persistent dilatation throughout the examination was implied; a transient apparent dilatation was not regarded as pathological.

Of the nine patients with dilatation of some part of the upper urinary tract six had suffered recurrent attacks of urinary infection, including the patient in whom a radiological diagnosis of chronic pyelonephritis was made. A urinary infection at the time of follow-up was found in one of the two patients with caliceal, pelvic, and ureteric dilatation, in both the patients with ureteric dilatation, but in none of the patients with caliceal dilatation alone.

Dilatation of the upper urinary tract in pregnancy is predominantly hormonal in origin, but is also due in part to pressure of the uterus on the ureters; the persistence of this dilatation for long periods after pregnancy cannot be explained by a continuation of either of these factors. It seems probable that infective fibrosis of the walls of the calices, pelvis, or ureter occurs during pregnancy, and this prevents the normal disappearance of the dilatation of these structures. This also would explain the frequency of persistent dilatation of the upper urinary tract (9/43) in patients who had suffered a urinary infection in pregnancy. Although infection

is more likely to persist in an abnormal urinary tract, dilatation of the calices, pelvis, or ureter does not necessarily indicate the presence of a chronic pyelonephritis.

The patient with a vesical diverticulum experienced recurrent attacks of cystitis during and after pregnancy. A small ureterocele was found in one patient who had cystitis before and during pregnancy. It is of interest to note that in another patient investigated after this series had been completed a large unilateral ureterocele was found which contained two calculi.

The fundus of the bladder normally presents a smooth and rounded outline in the intravenous pyelogram of the normal pregnant woman. The degree of convexity of this margin depends on the degree of bladder-filling.

Intravenous pyelogram of a patient delivered five years previously. No lesion is noted in either kidney or ureter, but the bladder shows a deep fundal impress.

Occasionally the uterus makes a shallow impress on the vesical fundus which may be more pronounced when the uterus is anteflexed and anteverted. In nine patients in the present series there was a wide and deep impression of apparently extrinsic origin on the fundus of the bladder (see Fig.) which was much larger than the impress made by a normal non-pregnant uterus. Examination of these patients revealed no pelvic tumour. It was thought that an enlarged uterus must be pressing on the bladder, but bimanual palpation and the passage of a uterine sound showed the uterus to be within normal limits of size or in one case slightly enlarged. The cause of the vesical impress has not been determined. The appearances strongly favour a slight increase in the bulk of the uterus without its cavitary length being increased. At the follow-up, urinary abnormalities were present in six of the nine patients showing this bladder impress, and three of these also had dilatation of the upper urinary tract.

Pyrexal Test

Pears and Houghton (1959) found that the intravenous injection of a bacterial pyrogen, pyrexal, into patients with chronic pyelonephritis increased the urinary cell count; this response may occur in patients with acute pyelonephritis but not in normal patients or in those with non-infective renal disease. The value of this test lies mainly in the detection of chronic renal infection when urine examination is otherwise normal; it was performed on 22 patients with either a history of recurrent urinary infection or of abnormal urinary or radiological findings at the time of follow-up. The method used for this investigation was similar to that described by Pears and Houghton.

The cell counts reported by Pears and Houghton did not differentiate between renal epithelial cells and leucocytes, and did not include squamous epithelial cells or red cells. We have counted all these types of cells separately, and it is apparent that different patients react to pyrexal with different cellular responses.

An increased urinary cellular excretion was found in 12 patients (Table IV), and five of these had a history suggesting recurrent renal infection. Nine had a urinary infection at the time of follow-up, but after treatment only four were still apparently infected when the pyrexal test was performed; this confirms that the urinary cellular response to the injected pyrogen may occur in the absence of obvious urinary infection.

TABLE IV.—*Patients With Increased Urinary Cellular Excretion After Injection of Pyrexal*

Case No.	History	Catheter Specimen of Urine at 5-Year Follow-up	History of Recurrent Renal Infection	Treatment with Antibiotic (Before Pyrexal Test)	Increase in Urinary Cellular Excretion After Pyrexal	Intravenous Pyelogram
1	Pyelonephritis in 2 pregnancies	Infection	−	+	Leucocytes, epithelial and red blood cells	Bladder dent
2	,, during and after 2 pregnancies	,,	+	+	,, ,, ,,	Systolic contraction of normal pelvis
3	,, ,, ,, ,, 3 ,,	,,	+	+	,, ,, ,,	Bladder dent
4	,, ,, ,, ,, pregnancy	,,	+	−	Leucocytes and epithelial cells	No appreciable disease
5	,, in 1st pregnancy	,,	−	+	,, ,, ,,	Dilatation right ureter and bladder dent
6	Urinary infection in 1st pregnancy. Symptoms in upper and lower urinary tract since	,,	+	+	,, ,, ,,	Relative stasis in right renal pelvis
7	Urinary infection in 4th pregnancy	,,	−	−	,, ,, ,,	No appreciable disease
8	,, ,, ,, 3rd ,, Symptoms in lower urinary tract since	Normal	−	−	,, ,, ,,	Not done. Allergy
9	Pyelonephritis in 1st pregnancy. Recurrent symptoms in lower urinary tract since	Infection	−	+	Leucocytes	No appreciable disease
10	Urinary infection in 3rd pregnancy. Symptoms in upper and lower urinary tract since	,,	+	+	,,	Bladder dent (Fig. 1)
11	Pyelonephritis in 1st pregnancy	Leucocytes and red blood cells	−	−	,,	No appreciable disease
12	,, ,, ,, ,, Symptoms in lower urinary tract since	Normal	−	−	,,	Bifid type left pelvis and calices

Although Pears and Houghton found an increased urinary cellular excretion after the injection of pyrexal in patients with chronic pyelonephritis, it is possible that a patient with any type of chronic urinary infection—for example, urethritis or cystitis—may respond in this manner. In this series the numbers of renal epithelial cells and leucocytes have been counted separately, for it was thought that if there was an increase in both the renal epithelial cells and the leucocytes after pyrexal the chronic urinary infection would probably be situated in the kidney substance. There was an increase of both these types of cell in eight patients and of leucocytes alone in four; the significance of this is not clear, but in four out of the five patients with chronic pyelonephritis an increase in epithelial cells was found. Ten patients had no significant change in the urinary cellular excretion rate after the injection of pyrexal, and none of these showed any clinical evidence of chronic urinary infection.

Discussion

Clinical examination of the patient is quite unreliable both for diagnosis and for estimating the results of treatment of urinary infection. Of the 10 patients in this series who at follow-up examination had undoubted urinary infection, only one had symptoms or signs attributable to it. A history of recurring episodes of urinary infection was more significant, being obtained on direct questioning in 8 out of the 10 patients.

Repeated examination of the urine for leucocytes and bacteria over a period of time is essential; the risk of causing infection by repeated catheterization can be avoided by using mid-stream instead of catheter specimens of urine. Stansfeld (1954) showed that the average number of leucocytes in the urine of 115 patients with chronic pyelonephritis was only 2–3 per high-power field, and that leucocyte counts of over 50/c.mm.—equivalent to about one in every 5–10 high-power fields—are rarely, if ever, encountered in normal urine. It is probable that only very small numbers of leucocytes in the urine should be regarded as normal; the presence of larger numbers must always be looked upon with suspicion and an attempt made to confirm their presence and determine their origin. Infection of the renal tract is usually associated with large numbers of bacteria in the urine; and although contamination also causes the presence of bacteria in the urine, infection can be distinguished from contamination by estimating the numbers of organisms in fresh specimens of urine, either by direct bacterial counts (Kass, 1957) or by counting the numbers of colonies that grow in culture (Wood *et al.*, 1960). True bacilluria, such as Kass showed to accompany acute pyelonephritis, always gives a very high bacterial count, while accidental contamination is associated with low counts only.

The pyrexal test was positive in 9 out of the 10 cases in which urinary infection was found at follow-up examination, whether or not subsequent treatment had rendered the urine sterile. It would seem that this test is a worth-while aid in the search for latent infections of the urinary tract. It is possible that differential counts of renal epithelial cells and leucocytes may help to locate the infection, high counts of renal epithelial cells suggesting that the kidney is involved.

Radiological studies are of value in revealing the presence of congenital and acquired abnormalities of the urinary tract, some of which are amenable to surgical treatment. The significance of the deep fundal indentation of the bladder found in nine of our cases is not yet clear.

It is difficult to obtain proof that the treatment of long-standing chronic pyelonephritis alters the course of the disease. Infection often recurs after treatment, and in these patients intrarenal changes and bacterial resistance of antibiotics may limit the effectiveness of treatment. As chronic pyelonephritis may begin in pregnancy, adequate care and follow-up of all pregnant patients with urinary infection may help to diminish the incidence of this disease.

Summary and Conclusions

A study has been made of 50 patients five years after a urinary infection in pregnancy.

Thirty-nine suffered from recurrent urinary infections. In 20 of these pregnancy had apparently initiated the infection.

There were abnormal radiological findings in 19 patients, and their significance is discussed.

Urinary infection was found in 10 of the 50 patients at the time of follow-up. Clinical evidence suggested that five of these were suffering from early chronic pyelonephritis; two others had undergone nephrectomy for unilateral chronic pyelonephritis, making a total of 14% of patients with chronic pyelonephritis in the series.

The pyrexal test was performed in 9 out of the 10 cases with active urinary infection at the follow-up examination, and was positive in them all.

The clinical state of the patient is unreliable in estimating the cure of a urinary infection, which is best determined by the persistent absence of leucocytes and organisms in the urine. The risk of causing infection by repeated catheterization can be avoided by the use of mid-stream urine. Chronic pyelonephritis may begin in pregnancy, and adequate treatment and follow-up of all pregnant patients with urinary infection may help to diminish the incidence of this disease.

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" Rather interesting stories lie behind the selection of some trivial names, as in the case of barbituric acid. This was the discovery of the chemist, Baeyer, who came upon the new compound as a combination of maleic acid with a breakdown product of uric acid. He wrote later that he was enamoured at the moment of a charming lady named Barbara, and so he decided to call the new compound " barbituric acid " in her honour. The story does not end there, for later the physician von Mehring took a trip to Italy shortly after discovering the hypnotic properties of diethylbarbituric acid, and, as he approached the city of Verona, he was struck with the idea of naming this compound Veronal." (Dr. LLOYD C. MILLER, Ph.D. (director of revision, *U.S. Pharmacopeia*), " Doctors, Drugs, and Names." *J.A.M.A.*, July 8, 1961.)

RETENTION OF URINE AND PROSTATECTOMY

A REVIEW FROM A SMALL PROVINCIAL HOSPITAL

BY

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> "When surgeons gather together to speak about retention of urine they all tell us how old their patients are. We never believe them. However, I would like to assure you that my patients are not only very old but are very very decrepit."
> —A. DICKSON WRIGHT.

Lee *et al.* (1957) contrasted the mortality for prostatectomy for "hyperplasia of the prostate" in teaching and non-teaching hospitals. The relative percentages were 6.2 and 17.1 in 1951, improving to 4.1 and 9.5 in 1953–4. They pointed out, however, that the teaching-hospital figures showed a smaller proportion of older age-groups and fewer "immediate admissions"—presumably cases with retention of urine. Riches (1950) quotes figures from specialist urological units with a mortality varying from 3.7% to 6%, but gives a figure of 28% for cases in a general hospital treated by suprapubic cystostomy. Bomford (1959) records a small series of patients with retention, with a mortality of 13% (7 out of 55), but only four of the seven had had prostatectomy, and he does not give the proportion of cases treated by prostatectomy or other methods. Ellis and Leatherdale (1958) report a mortality of 10.7%. Their series, however, is a selected one, as they cover only those cases thought fit for a one-stage prostatectomy—in fact, they advocate permanent suprapubic or catheter drainage in the poor-risk case (see below).

McEachern (1958) gives the mortality "from diseases of the prostate excluding carcinoma" for Australia in 1954 as 14.3% and reviews a personal series of 222 consecutive cases, with a mortality of 6.7%. His mortality for cases of retention submitted to prostatectomy was 7.8% (13 deaths in 165 cases), whereas the mortality was only 3.5% (2 deaths in 57 cases) in patients without retention. He does not discuss those cases admitted with retention who were unfit for prostatectomy. McEachern's series is very similar in number of composition to the present one. This comprises those patients suffering from retention of urine or from symptoms attributable to prostatic enlargement who were admitted to the general surgical wards of a small hospital under the care of one surgeon in a provincial town in Northern Ireland during the period 1955–9. In this five-year period 197 patients were admitted with prostatic disease. Of these, 140 were cases of retention and 57 were patients with signs and symptoms of prostatic disease without retention who were admitted for interim prostatectomy. Of these 197 men, 28 (14.2%) died, but 27 of the deaths occurred in those presenting with retention—only one death resulted from "cold" prostatectomy (Table I).

TABLE I.—*Cases of Prostatic Disease, With Mortality Rate and Average Age*

	All Cases		Fatal Cases	
	No.	Average Age	No.	Average Age
With retention ..	140	71·7 years	27 (19·3%)	78·8 years
Without ,, ..	57	69·0 ,,	1 (1·8%)	73 ,,
Total ..	197	70·9 ,,	28 (14·2%)	78·6 ,,

Social Background

Before considering further this appallingly high mortality rate the social and hospital background must be explained. The area served by the hospital is predominantly a farming one. The men often refuse to attend hospital until the onset of retention. If the "immediate admissions" of Lee *et al.* (1957) include all retentions, as they presumably must, then a maximum of 44% of teaching hospital cases and 61% of non-teaching hospital cases have retention. In the present series 71% had retention on admission; a figure comparable with that of McEachern (1958), who had 74% in his Australian series.

In many instances patients were admitted only after the failure of relief following catheterization by their own doctor. Of the 140 cases, 61 (43.6%) had been catheterized at least once before admission. In McEachern's series only 15% had been catheterized outside hospital.

This delay in attending is shown also by the relatively low proportion of interim prostatectomies, although this is not the reason for the marked difference in mortality in the two groups. There is obvious selection in those cases seen at the out-patient clinic with prostatism—only the relatively fit case or the one who could be made fit being subjected to operation in the absence of retention. However, the average age of the two groups is not really different (Table I).

A further social consideration explains why 133 of the 140 cases of retention were treated by prostatectomy. It is realized that many of those who died after prostatectomy might have survived (for a few weeks or months) with simple suprapubic drainage, but many of these old men were living alone or with an equally aged spouse, and the management of a permanent suprapubic catheter under such social circumstances is well-nigh impossible. This is epitomized by my medical colleague in writing of a patient who was initially under his care with cardiac failure and who had a suprapubic cystostomy done elsewhere two months before. The patient died after prostatectomy, and Dr. E. L. Wilson, in the letter to the general practitioner, says, "This was too much for him. One cannot, however, really regret that this step was taken, since he found life, as he was, intolerable." Similarly, McEachern (1958) says, "Many of these cases should have had no more than a permanent suprapubic cystostomy, but it is felt that this is often unacceptable in modern society."

The hospital concerned has no bacteriological, haematological, or biochemical laboratory attached, and, although a very efficient service in these specialties is provided from a centre 40 miles (64 km.) away, there is an inevitable delay in obtaining the results of investigations. For this reason routine pre- and post-operative urine cultures, blood urea, etc., have not been done and the clinical assessment of the individual patient has had to be relied upon in most cases. Similarly, although a small blood bank is kept in the hospital, operation sometimes had to be delayed until the patient's blood group was known and suitable blood made available.

The main drawback was the delay in the receipt of the results of the sensitivity of the infecting organisms to the various antibiotics in the obviously infected cases.

Retention of Urine

Table I shows that prostatectomy for prostatic lesions without retention appears to be a safe operation, and the following discussion is mainly concerned with those cases in which retention of urine was the presenting symptom. These number 140 and do not include several cases of retention after over-indulgence in alcohol where normal micturition returned after a single catheterization and a long sleep. Nor do they include cases of retention due to stricture or neurological lesions. They may be divided into acute and chronic. Acute retention is here defined as retention of urine with a painful, tender, enlarged bladder. Chronic retention is reserved for those cases with a non-painful, distended bladder and uncontrollable dribbling incontinence which had been present for some time—often for weeks. The fact that 18 (12.9%) of the cases were chronic retention (Table II) again shows the delay in seeking medical advice in this series, especially as the man with a large residual urine but no incontinence is not included in the chronic-retention group.

TABLE II.—*Mortality Rate With Various Types of Treatment*

	Acute Retention		Chronic Retention		Interim Prostatectomy	
	Total	Deaths	Total	Deaths	Total	Deaths
Total	122	22	18	5	57	1
Catheter drainage only	2	2	1	1	—	—
Suprapubic cystostomy only ..	4	3	—	—	—	—
Prostatectomy ..	116	17	17	4	57	1
Retropubic prostatectomy ..	76	10	11	2	40	1
Transvesical one-stage prostatectomy	23	2	5	2	17	—
Fryer two-stage prostatectomy	17	5	1	—	—	—

Mortality for retention of urine, 19·3%. Mortality for prostatectomy for retention, 15·8%. Mortality for prostatectomy (all cases), 11·6%. Mortality for prostatectomy without retention, 1·8%.

Initial Treatment

Immediate prostatectomy as the treatment of choice has not been the practice in this hospital's series. The difficulties of staffing—medical, theatre, and nursing—and the absence of laboratory services preclude this. Also, many of the cases in this series fell into the groups III and IV of Wilson Hey (1945) and even in his hands had a mortality of 16% and 66%.

The initial treatment of the case with retention of urine depended on the initial clinical assessment, and four main groups are easily recognized.

1. *The healthy old man with no gross cardiovascular lesion.*—In these cases catheter drainage was instituted, followed by prostatectomy in two to four days. If catheterization was not possible (a not uncommon sequel of repeated catheterization outside hospital) drainage was done by means of a Riches suprapubic tube. The delay before operation may be criticized, but was necessary to confirm the clinical assessment, to check on renal function in doubtful cases, and to arrange for blood for transfusion if necessary.

2. *The patient with some other lesion who was thought unfit for early operation but thought to be capable of being made fit for operation in 10–14 days.*—Included were cases showing moderate hypertension and a history of old cerebral lesions, cardiac irregularities without failure, severe bronchitics, obvious cases of anaemia, and cases with mild uraemic symptoms. In this type of case a Riches suprapubic tube was inserted or, under local anaesthesia, a small-bore de Pezzer catheter was introduced suprapubically.

3. *The very ill man who was going to require a long period of medical treatment before he was even "fairly fit" for surgery.*—In this group, which comprised cases of cardiac failure, recent hemiplegia, and renal failure, a suprapubic drainage was done under local anaesthesia—sometimes after preliminary catheter drainage.

4. *The moribund.*—In these cases a catheter was passed and tied in. Sometimes the apparently hopeless case improved and moved into the third group.

The initial treatment did not differ in the acute and the chronic retention except that in the latter even more care was paid to slow decompression.

Definitive Treatment

Table II lists the treatment and types of operation performed. Cases in group 1 above were treated by retropubic prostatectomy or by transvesical prostatectomy if cystoscopy revealed an intravesical lesion—diverticulum, neoplasm, or stone. Group 2 cases were treated by the retropubic approach in some but usually by a transvesical operation with closure of the bladder (Harris). If cases in groups 3 and 4 responded to treatment the prostate was removed by blind enucleation through the suprapubic wound. Transurethral prostatectomy was not used.

It will be seen that seven patients did not have a prostatectomy and six of them died. Of the three who did not have an operation, one who had been transferred from the medical ward where he had been treated for cardiac failure died during the induction of the anaesthetic; the second had a carcinoma of the recto-sigmoid and refused operative treatment; and the third died a few hours after admission.

Four patients had only a suprapubic cystostomy and three of these died in hospital. The fourth refused further treatment and died nearly four months later, at home, from renal failure, probably due to ascending infection. Of the three who died in hospital, two were transfers from the medical wards who had developed retention while under treatment for cardiac failure, and the third had a recent hemiplegia due to cerebral thrombosis. One died the day of operation, the others died two and seven days later.

On the remaining 133 patients a prostatectomy was done with 21 (15.8%) deaths. The mortality after retropubic or transvesical one-stage operation was roughly the same, but was higher after the two-stage Freyer operation. This is to be expected, as more poor-risk cases are included.

Similarly, the period in hospital (Table III) was longer after the two-stage operation than after a retropubic or closed transvesical operation, but the post-operative stay in hospital did not materially differ in

TABLE III.—*Duration of Hospital Stay (In Days)*

	Pre-operative	Post-operative	Total Stay*
Retention surviving prostatectomy ..	7·3	19·8 { R—17·1 T—22·3 F—28·9	28·1
Fatal cases	8·7	11·3	21·0
Interim prostatectomy ..	3·1	16·9	21·0

R = Retropubic prostatectomy. T = Transvesical one-stage prostatectomy. F = Freyer two-stage prostatectomy.
*Day of operation included.

the interim prostatectomy cases and those cases of retention surviving after one-stage prostatectomy. McEachern (1958) gives his average stay in hospital as 27 days, Bomford (1959) as 37 days, but Wells (1953) says "the ordinary good risk case is ready for discharge and fully ambulant in under 14 days." The average stay in hospital for cases submitted to prostatectomy in this series (excluding fatal cases) was 25.6 days.

Pathology

All specimens were examined microscopically, histological findings being shown in Table IV. Carcinomatous change was found in 26 out of 190 (13.7%)—a figure lower than that of Young (1945), who had

TABLE IV.—*Histological Findings and Mortality Rates*

	Retention		Without Retention		Total	
	Total	Deaths	Total	Deaths	Total	Deaths
Benign hyperplasia .. Fibrosis.	100	16	47	1	147 (77·4%)	17 (11·6%)
Median bar	2	—	4	—	6 (3·2%)	—
Benign hyperplasia with abscess or severe infection ..	10	1	1	—	11 (5·7%)	1 (9·1%)
Carcinoma ..	21	4	5	—	26 (13·7%)	4 (15·4%)

21%, and of White and Berry (1950), who had 16%, but much higher than McEachern's (1958) figure of 7.6%. White and Berry (1950) suggest that 9 out of 10 carcinomas of prostate may be diagnosed by rectal examination. Only 4 of the 26 proved cases here were diagnosed, with confidence, before operation. Two of these (one without retention) were thought suitable for total prostatectomy. The other two cases had retention but did not respond to oestrogens and had a transvesical diathermy excision of the prostate. In many cases the histological diagnosis came as a complete surprise (the so-called occult carcinoma). In other cases the diagnosis was suspected before or confirmed at operation when difficulty in enucleation of a hard nodule or fixation of part of the prostate was found. Conversely, cases have been encountered where the findings at operation suggested malignancy but the pathologist reported only fibrous or inflammatory change.

All cases suspected before or at operation were started on oestrogens (castration was used rarely except in late relapses). "Occult" carcinoma was treated in the same way. The numbers are small but they do show a higher mortality in the malignant cases. The large number showing severe infection, usually with local abscesses (5.7%), may be due to the large number of cases which had been catheterized before admission or, possibly, to the delay between admission and prostatectomy.

Coexistent Lesions

Additional surgical conditions treated at the same time as the prostatectomy were: papilloma of bladder in two cases, diverticulum of bladder in six, stone in bladder in eight, and hernia in 12. The importance of immediate pre-operative cystoscopy is illustrated by the finding of two unsuspected papillomata in cases of acute retention. Similarly, the presence of diverticula can be confirmed and a decision reached on whether diverticulectomy should be done. The shallow diverticulum with a wide mouth need not be resected, but the larger ones with narrow orifices must be removed if serious subsequent trouble is to be avoided. Small non-adherent diverticula can be removed by invagination and division of the neck, but larger ones, and especially where infection is present, are excised by a combined transvesical and extravesical approach (Badenoch, 1953). Six cases, all with more than one diverticulum, were thus dealt with in the series. One further example was missed (see below).

Stones in the bladder were found in eight cases—two of these also had stones in a diverticulum. One man who had lived for 13 years with a suprapubic tube which he changed himself had 97 stones in his bladder when he was at last persuaded to have a prostatectomy. Despite a long and stormy convalescence and the development of an incisional hernia, he now comes into the category "very grateful patient."

Many of these old men have inguinal herniae, and, unless the general condition is very poor, it is my custom to treat the hernia at the same operation. This was done in 12 out of the 190 cases (two were bilateral) without any ill effects. The cord was divided in all cases and the canal closed. The operation can be done easily by a short extension of the transverse incision now used as a routine for one-stage prostatectomy. In addition to the 12 cases with inguinal hernia, one case had an irreducible femoral hernia which was dealt with through a separate incision.

Post-operative Complications

Of the 168 patients surviving after prostatectomy, 32 (19%) had one or more of the post-operative complications listed in Table V, but in no case did death result from the complication. Of these complications, stricture of the urethra was the commonest (7.1%). Eight of these were post-meatal strictures, three were posterior strictures, and one occurred in the penile

TABLE V.—*Post-operative Complications (Surviving Cases)*

Stricture — Post-meatal	8 (4·8%)	Incontinence	4 (2·4%)
Stricture — Other ..	4 (2·4%)	Incisional hernia ..	10 (6·0%)
Epididymitis	8 (4·8%)	Stone in bladder ..	3 (1·8%)
Osteitis pubis	3 (1·8%)	Bladder diverticulum	1

urethra. Johnston (1953) found a 20% incidence of post-meatal stricture. Ross and Tinckler (1959) had only two cases in 100 consecutive prostatectomies. They attributed the lowered incidence to the avoidance of red rubber catheters, and my experience agrees with this supposition, as only one case has been encountered in the last three years under review since a latex two-way catheter has been used post-operatively. Although relatively common, the post-meatal stricture is not a serious complication if recognized, and only two cases required more than two dilatations before permanent relief was obtained. This confirms McEachern's (1958) comment.

Stricture in other parts of the urethra is a more serious problem. The patient with the stricture in the penile urethra, the cause of which is not known, was cured by excision of the stricture and is now symptom-free, but the three patients with posterior strictures still attend at varying periods for dilatation. All three followed a two-stage prostatectomy.

About a year after the present series was started routine division of the vasa deferentia was discontinued because two successive cases developed epididymitis despite vasostomy. This policy persisted for only a few months, until Caine's (1954) paper was brought to my attention.

He reported epididymitis in 7% when the vasa were tied and in 25% when the operation was omitted. Thus the vast majority of the one-stage prostatectomies in this series had bilateral ligation and division of the vasa (the exact number cannot be given because all the operation records do not include sufficient detail). Ross and Tinckler (1959) also report a 7% incidence, which is higher than in the present series (4.8%), where three of the eight cases occurred after two-stage prostatectomy—division of the vasa was not done in conjunction with this type of operation. Included in the remaining five cases is one in which an abscess formed at the vasotomy operation scar without a true epididymitis occurring.

Ross and Tinckler (1959) had no case of osteitis pubis in 100 cases and Millin (1953) mentions only 13 in over 2,000 retropubic prostatectomies. There were three cases in the 190 prostatectomies under review, but two of these were not confirmed by radiological examination. In only one case was the pain severe and incapacitating, with *x*-ray evidence of bony disease. This followed a retropubic prostatectomy for acute retention, and it was six months before the patient was symptom-free.

Although not usually mentioned in the textbooks, some degree of incontinence is not infrequent after all types of prostatectomy. Ross and Tinckler (1959) found a temporary incontinence in 25% of prostatectomies, more common in the older age-groups, and clearing "in the course of weeks." They had no case of permanent incontinence. When the four patients listed in Table V were seen at the follow-up clinic three months or more after operation they still had not regained full control. Many others had had some trouble in the first few weeks after discharge from hospital, but, when seen, had returned to normal. Two of the cases of incontinence followed diathermy excision for carcinoma of the prostate, one followed a two-stage prostatectomy, and the fourth, in which incontinence occurred only on coughing or straining, followed a "cold" retropubic prostatectomy. The two patients with carcinoma died within a year of operation but were maintained in a fair degree of comfort by the use of Paul's tubing and a urinal. The "stress" incontinence patient refuses any appliance, and the fourth patient, a feeble old man in the middle eighties, used a penile clamp until his death from cerebral thrombosis 18 months after operation.

The above complications occurred soon after prostatectomy. Late complications due to the operation consisted of persistent or recurring attacks of frequency with pain or the development of an incisional hernia. In three of the cases of recurring cystitis a stone was found in the bladder: two of these followed a two-stage prostatectomy. In the same period three other cases of bladder-stone after Freyer's prostatectomy, done in other hospitals, were seen. Three questions arise: Were these stones present when the initial operation (essentially a "blind" one) was done? Were they formed round a prostatic stone or loose tag from the prostatic fossa? Or, as seems more likely, was a nidus provided by blood clot and the inevitable infection which followed Freyer's prostatectomy? In all cases relief followed removal of the stone. In one case a persistent pyuria and intermittent breakdown of the suprapubic wound was found to be due to an overlooked bladder diverticulum. Its removal presented what Badenoch (1953) described as "a Herculean task," which fortunately was successful, but illustrated the importance of careful pre-operative examination. Only one case of incisional hernia has followed the use of a transverse incision for one-stage prostatectomy, which is now practised routinely but was used in only approximately 50% of the cases reviewed. Four cases followed retropubic prostatectomy using a midline incision and five followed a two-stage prostatectomy. Only three out of the 10 patients complained of discomfort, and their symptoms were relieved by a surgical support. In no case was operative repair advised.

It will be seen that, although nearly one in five cases had some complication, very few were seriously incommoded by the complication, and, excluding the cases of incontinence, were satisfactorily dealt with. It will also be seen that a large proportion of the complications followed the two-stage operation.

Causes of Death and Predisposing Factors

Post-mortem examinations were not made in any of the fatal cases, and the causes of death given in Table VI were based on the clinical findings. In one of the six fatal cases where prostatectomy was not carried out, the patient, as stated above, died from a carcinoma of the recto-sigmoid with secondaries in the lungs and is not included in Table VI.

TABLE VI.—*Causes of Death*

	Total	Post-prostatectomy
Cardiac failure or coronary thrombosis	10	7
Renal failure	5	5
Massive pulmonary embolus	2	2
Cerebral thrombosis	5	3
Cause unknown	5	5

Of the five other cases, treated by drainage only, three were cases with cardiac failure transferred from the medical ward, one was a hemiplegic also from the medical ward, and the fifth was an old man with a recent cerebral thrombosis who died a few hours after admission for treatment of his retention. Of the fatalities occurring after prostatectomy, cardiac disease was the commonest diagnosed cause. Four apparently fit men died from coronary thrombosis which was confirmed by E.C.G. Two others who had previously had a proved coronary thrombosis died with symptoms suggestive of further coronary infarction. One patient developed severe cardiac arrhythmia and, despite treatment, died of circulatory failure.

Renal failure as evidenced by oliguria, signs of uraemia, and a climbing blood urea was designated as the cause of death in only five cases, but it is felt that it was probably a major factor in the "cause unknown" group and a contributory factor in several other cases. Certainly many of the other cases showed some evidence of renal failure, usually with signs of severe infection. Pulmonary embolus and cerebral thrombosis as causes of death need not be enlarged upon—they are inevitable sequelae of operations on feeble and often inactive old men.

In those patients with retention on whom bladder drainage, by catheter or suprapubic cystostomy, was the only treatment, an obvious cause of death was present before the onset of retention. Similarly, 12 of those dying after prostatectomy had had previous severe cardiovascular lesions (necessitating hospital treatment in six cases) and four of these also had a chronic respiratory infection (Table VII). They were

cases where a major operation was accepted as a calculated risk and a fatal outcome was not unexpected by patient, doctor, or relatives. However, perusal of the case histories provides no evidence of any serious previous disease necessitating treatment in hospital or by their own doctor in 10 cases. Although most of

TABLE VII.—*Previous History of Those Who Died After Prostatectomy*

	Total	Transferred from or Previously Treated in Medical Ward
Severe cardiac lesions ..	9	5
Hemiplegia	3	1
Severe bronchitis	4	2
Nothing of note	10	—

them had some degree of arteriosclerosis they were apparently fit men who were "killed by the operation." As stated above, four of these deaths resulted from coronary thrombosis, but it is interesting to note that, of the other six, four died of renal failure and two from "causes unknown." Furthermore, although 44% of all the cases admitted with retention had been catheterized before admission, 17 (81%) of the 21 deaths after prostatectomy for retention had previously been catheterized (often repeatedly), including this particular group of six.

Summary and Conclusions

A review is presented of 197 cases of prostatic disease admitted to the surgical wards of a small provincial hospital over the five-year period 1955–9, with, in particular, a consideration of the fatalities.

Prostatectomy for prostatic disease without retention has a low mortality, and earlier operation for milder degrees of prostatism, before the serious consequences of the disease are manifest, would seem to be the only way to reduce materially the overall mortality.

Too many cases of prostatic disease to-day present with retention, and although a two-stage operation is often the best treatment for these cases this method carries a higher mortality and morbidity rate than does the one-stage prostatectomy. More cases would be fit for one-stage prostatectomy if referred to hospital sooner than is the custom now.

Any operative procedure in the older patient must entail risk, and if, as a general principle, surgical treatment aims at a return to normal physiological function as opposed to merely preserving life, then additional risk and a higher mortality must be accepted—not only by the patient (who is usually only too willing to accept the risk) but also by the surgeon. Having accepted this calculated risk any method of reducing it must be searched for, and study of the cases in this series suggests two possible approaches. Firstly, the education of the public and the general practitioner regarding the dangers of the use of a catheter except in a hospital theatre. Secondly, the organization of the hospital services so that these cases can be dealt with as emergencies with bacteriologist, biochemist, etc., available as easily as is surgeon, physician, and anaesthetist.

In essence, this paper is a plea for the establishment of a specialized urological service. Although it is realized that general surgeons, such as myself, will miss the joy of having the survivor telling him that "I feel 20 years younger," there would be *more* survivors if these cases were treated in the equivalent of the teaching hospital of Lee *et al.* (1957).

It is a pleasure to thank Dr. E. L. Wilson, my medical colleague, for his invaluable help in many of these cases; also Dr. J. E. Morison for his guidance in the pathological reports; and Sister Martin and her nurses, whose care has often meant the difference between success and failure. I am indebted to a succession of house-surgeons (now scattered all over the world) on whom so much of the post-operative care devolved, especially the enthusiastic young lady house-surgeon who counted the 97 stones in the bladder. My registrar during this period, Dr. R. Stinson, has been a most helpful assistant and has had most of the responsibility for the day-to-day treatment. Finally, I wish to thank my secretary, Miss M. Acheson, for her assistance in collecting the records necessary for the production of this review.

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URINARY INFECTION IN CYSTOSCOPY

BY

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There is a good deal of evidence that one of the major factors in the aetiology of infections of the urinary tract is urethral instrumentation (Beeson, 1955–6). Gillespie *et al.* (1960) have shown the part played by catheterization and instrumentation in the production of urinary infections after prostatectomy. They have clearly indicated that by the proper sterilization of cystoscopes and the adoption of a closed system of catheter drainage the incidence of post-prostatectomy infections fell from 80% to 6%. Marple (1941) and Slade and Linton (1960) have investigated the role of catheterization in female patients in producing urinary infections; and Slade and Linton advocate that specimens of urine from female patients should be obtained by collecting a mid-stream specimen and not by catheterization.

It was the purpose of this investigation to determine to what extent routine cystoscopic examination, which is so often performed as an out-patient procedure, resulted in urinary infections.

Methods

The study was performed on a consecutive series of male patients who underwent a cystoscopic examination in the urological out-patient department of the London Hospital. The majority of them had been treated previously for a papilloma of the bladder and attended for follow-up examinations. Their ages varied from 33 to 75.

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A specimen of bladder urine was collected through the cystoscope and examination of the centrifuged deposit for leucocytes and organisms was performed. The deposit was also cultured for bacteria. A mid-stream specimen of urine was collected four days later and was examined in the same way.

The procedure of cystoscopy and the method of sterilization of cystoscopes employed in the urological department of the London Hospital are described, as these vary greatly in different clinics. The cystoscopes are sterilized by boiling in distilled water for five minutes. The telescopes are not boiled, but are sterilized by immersing them vertically in a solution of equal parts of 1:2,500 chlorhexidine ("hibitane") and 1:1,000 oxycyanide of mercury (Miller *et al.*, 1958). The irrigating solution consists of 1:5,000 chlorhexidine. The patients are examined in the lithotomy position in a cystoscopy chair and no sterile towels are used. The glans penis is swabbed with saline and the urethra is anaesthetized by two instillations of 2% "xylocaine gel" at an interval of five minutes. A penile clamp is applied after each instillation to retain the anaesthetic agent in the urethra. The surgeons wear a clean waterproof apron and wash their hands so that they may be clean but not sterile. No gloves are worn. Care is taken that only the proximal end of the instrument is handled and that the tip of the cystoscope is introduced directly into the urethra.

Results

During the period of investigation 110 cystoscopic examinations were performed on 84 patients (23 were examined twice and a few on three occasions). On 96 occasions (88%) the urine was found to be uninfected both before and four days after cystoscopy (see Table). In two instances the urine was found to have become infected after cystoscopy. In each case a moderate number of leucocytes and a moderate growth of organisms on culture were found in the second specimen of urine. In the first case the infection was due to *Streptococcus faecalis*; this cleared spontaneously during the next two weeks without any treatment. In the second case the infection was due to *Escherichia coli* and *Proteus vulgaris*. The patient had a papilloma at the time of the examination, and his infection cleared up after fulguration of the papilloma and the administration of alkalis and did not recur. These infections were both asymptomatic. It must be mentioned, however, that the presence of a papilloma does not appear to predispose to an infection, as 18 other patients in this group had papillomata present at the time of cystoscopy and they did not develop urinary infections.

Table of Results

	No.	No. of Patients
Cystoscopic examinations	110 (100%)	84
Urine sterile before and after cystoscopy	96 (88%)	73
,, infected after cystoscopy	2 (<2%)	2
,, found infected before cystoscopy	12 (11%)	9

On 12 occasions (nine patients) an existing urinary infection was present at the time of the original examination, which persisted. It was thus interesting to find that about 11% of patients undergoing follow-up cystoscopy in this clinic were suffering from an asymptomatic urinary infection.

These nine patients have been carefully investigated and in six of them an adequate cause for the persistent infection was found. In the remaining three the infection is unexplained and quantitative bacteriology has shown it to be significant, there being more than 3,000 organisms per ml. (Gillespie *et al.*, 1960). These infections have persisted despite various courses of treatment. The patients, however, are perfectly well, and it is difficult to persuade them to attend the clinic, as they have no complaints. At least two of the patients in this group have had a persistent asymptomatic urinary infection for four and six years without any apparent ill-effects, and they both have a normal blood urea and intravenous pyelogram.

Discussion

Opinions vary greatly over the dangers of instrumentation and catheterization in producing urinary infections. Beeson (1955–6), in a comprehensive survey of factors concerned in the pathogenesis of pyelonephritis, felt that the frequency with which catheterization and urethral instrumentation are performed indicates that many clinicians believe the danger to be small. There is in fact a lack of factual information on the frequency with which these procedures give rise to urinary infections.

In studies by Kass (1956) and Kaitz and Williams (1960) a significant number of male patients, selected at random and attending a general hospital for a variety of reasons, were found to have an asymptomatic bacteriuria. Their figures respectively were 4% and 10% of such patients. They found that nearly all these patients had undergone previous urethral instrumentation or catheterization. These findings correspond with the 11% of cases with existing urinary infection at the time of cystoscopy in this study. Two-thirds of these patients, however, had some abnormality of the urinary tract to account for this.

This investigation indicates that cystoscopy appears to carry little risk of producing a serious urinary infection. In both cases which developed an infection subsequent to cystoscopy the infection cleared fairly quickly, one spontaneously within two weeks, the other after treatment of his papilloma. Although in 12 examinations (nine patients) there was an existing urinary infection, some of which may have been the result of previous instrumentation, no fresh case of persistent urinary infection occurred in the remaining 98 cystoscopic examinations (75 patients). The persistence of the infection in these nine patients despite medical treatment is in accordance with the findings of Garrod *et al.* (1954), who showed that patients who had urinary infections associated with abnormalities of the urinary tract responded poorly to treatment with chemotherapy.

Ørskov (1952) felt that cross-infections occurring in the urinary tract were largely due to inadequate sterilization of instruments. Gillespie *et al.* (1960), as has already been mentioned, stress the overriding importance of effective sterilization of instruments. In the case of cystoscopes, sterilization by boiling is felt by many to be the ideal method (Winsbury-White, 1959). This is the procedure employed in this clinic, together with that advocated by Miller *et al.* (1958) for the telescopes, and it appears to be satisfactory. This study confirms that the sterilization of the instrument is the most important factor in preventing urinary infection, and that if this is properly carried out the precautions of "scrubbing up" and the draping of the patient with sterile towels appears to be unnecessary.

I think it is fair to say that cystoscopy performed with an adequately sterilized instrument does not appear to carry a serious risk of infection.

Summary

A study has been made of the incidence of urinary infection following a routine cystoscopy on 110 occasions in the out-patient department. In 11% of the patients an established asymptomatic urinary infection was found before cystoscopy. This is discussed.

The risk of cystoscopy producing a serious urinary infection appears to be slight, less than 2%, provided adequate precautions are taken for sterilization of the instruments.

I thank Miss P. Bretton, sister in charge of urological out-patients, for her invaluable assistance in this investigation; also Mr. G. C. Tresidder and Professor V. W. Dix for their helpful advice and criticisms. I am grateful to Dr. H. B. May and the staff of the clinical laboratory for carrying out the examinations of the urine specimens.

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CARBOHYDRATE AND SODIUM METABOLISM IN PERIODIC PARALYSIS

BY

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It has long been recognized that the administration of glucose, with or without insulin, will usually precipitate weakness in a person with periodic paralysis. The finding of a flat oral glucose-tolerance curve in such people by Aitken *et al.* (1937) and by Tyler *et al.* (1951) also suggests that their carbohydrate metabolism may be abnormal. The significance of these findings was largely neglected until MacGregor and Shaper (1957) confirmed the presence of a flat oral glucose-tolerance curve and also demonstrated hypoglycaemia unresponsiveness in a patient with the sporadic form of periodic paralysis. These authors believed that there was increased peripheral uptake of glucose in cases with periodic paralysis and that abnormality in glucose storage was important in the reduction of serum potassium levels and in the production of paralysis. However, the evidence was slight and the possibility of delayed intestinal absorption as the cause of the flat oral glucose-tolerance curve was not excluded.

The discovery that sodium retention often precedes attacks of paralysis (Conn *et al.*, 1956) suggested that an abnormality of sodium metabolism might be the primary disorder in this condition. However, sodium retention does not always precede attacks (Jones *et al.*, 1959), and the protective effect of a low sodium intake cannot always be demonstrated (de Graeff and Brocker, 1958).

The present study of members of a family with familial periodic paralysis was undertaken to reinvestigate carbohydrate metabolism in this condition and to re-examine abnormalities of sodium and creatine metabolism which have previously been reported.

Clinical Details

Four members of the family were studied.

The father, aged 45, had his first attack of paralysis at 6 years of age. Attacks reached a maximum frequency (three or four a week) when he was between 16 and 19 years and have since diminished to one or two monthly. The longest attack occurred at age 19, when he remained paralysed for six days.

A twin son (Antony) and daughter (Susan), aged 14, had their first attack on the same day when aged 3 years, after a long train journey. Antony is the more severely affected and suffers six or seven attacks weekly. Susan has three or four attacks weekly. The twins have always received potassium chloride (up to 24 g. daily) for their attacks. As a result the maximum duration of a single attack is only 48 hours.

The fourth member studied, the only other sibling, is a brother (Peter) aged 10 years, who has never suffered attacks.

All affected members display the typical features of attacks of periodic paralysis. They often wake with complete paralysis of the limbs and trunk. Some movement of the head and neck is always possible, and bulbar and sphincter disturbances have not occurred. Examination at these times shows flaccid paralysis of all limbs with absent tendon reflexes. Less severe attacks can occur at any time of the day, and in some attacks isolated muscle groups were affected alone. Even between attacks muscle strength is impaired. Paralysis is more severe in cold weather, and each affected member recognizes that carbohydrate ingestion is likely to precipitate paralysis.

Methods

Glucose Tolerance

All tests were performed in the early morning after an overnight fast. The subjects were on a normal diet containing 200–300 g. of carbohydrate daily except for the three final oral glucose-tolerance tests performed on Susan when she was on a balance diet containing about 125 g. of carbohydrate.

Oral glucose-tolerance tests were performed using 100 g. of glucose. Venous blood was taken just prior to the administration of glucose and half-hourly for two hours thereafter. On one occasion a Miller–Abbott tube was passed into the jejunum of Antony, its position being confirmed by *x*-ray examination, and 100 g. of glucose in 150 ml. of water delivered into the small bowel.

Intravenous glucose-tolerance tests were carried out by the method of Amatuzio *et al.* (1953). For each test a glucose-disappearance rate was calculated.

Insulin-sensitivity tests were made using 0.1 unit of soluble insulin per kilogram of body weight injected

intravenously, and the blood glucose was followed at intervals of 10 to 15 minutes for two to two and a half hours.

Serial E.C.G. tracings were made during most of these tests. Lead V3 was found to be the most sensitive to changes in the serum potassium levels and was mainly used.

The serum potassium level was estimated serially during all of these tests. Antony received daily supplements of 12–20 g. of potassium chloride throughout the study period. Susan received 3–4 g. of potassium chloride as necessary to relieve weakness.

Paralysis was produced by withholding the evening dose of potassium and substituting 100 g. of glucose at 9 p.m. The attacks during which glucose tolerance was tested were characterized by severe weakness, absent tendon jerks, and serum potassium levels below 3.2 mEq/l.

Blood glucose was estimated by the method of Asatoor and King (1954).

Balance Studies

Susan was given a diet containing 22 mEq of sodium and 80 mEq of potassium daily throughout the trial period of 50 days. A constant supplement of 26 mEq of potassium was given daily as potassium chloride capsules. The sodium intake was varied by the addition of sodium chloride capsules. For the first 15 and the last 7 days of the balance period the total daily sodium intake was 126 mEq. On the other days the total daily sodium intake was 22 mEq. Urine was collected over 12-hour periods from 6 a.m. to 6 p.m. and from 6 p.m. to 6 a.m. Each specimen was analysed for sodium, potassium, creatinine, and creatine.

Results of Glucose-tolerance Tests

Figures for these tests are given in the Table or in Fig. 1.

Antony.—On two occasions oral glucose-tolerance tests were performed with the patient on a high potassium intake. These showed flat curves, but no change in the serum potassium levels was observed and paralysis did not appear. The same tests performed with the patient on a normal potassium intake invariably caused a fall in serum potassium, with paralysis. To investigate the cause of these flat curves 100 g. of glucose was delivered into the small bowel via a Miller–Abbott tube. Paralysis began at 10 minutes and was complete at 25 minutes. Over this period the blood glucose level did not rise. The changes in the E.C.G., serum potassium, and blood glucose are shown in Fig. 1. The early changes indicate that delayed intestinal absorption of glucose is not the cause of the flat oral glucose-tolerance curve. Intravenous tolerance tests were performed on four occasions—two during attacks of paralysis and two within eight hours of recovery from paralysis. During attacks the glucose disappearance rate was normal, but after attacks an abnormally low disappearance rate was seen. A normal response to insulin was observed during one attack of paralysis, but on the one occasion when tested between attacks hypoglycaemia unresponsiveness was demonstrated.

Susan.—On a normal diet 100 g. of glucose similarly produced a flat oral glucose-tolerance curve and precipitated a severe attack. On a restricted carbohydrate intake 100 g. of glucose on two occasions produced

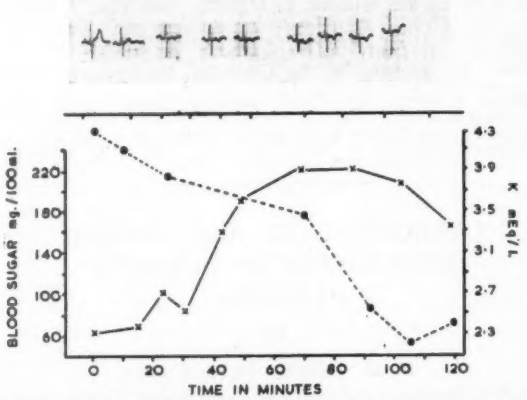

FIG. 1.—Effect on the E.C.G. and serum potassium (- - - -) and blood glucose (———) levels of 100 g. of glucose delivered into the jejunum at time 0 minute. Paralysis began at 10 minutes and was complete at 25 minutes.

Results of Glucose-tolerance and Insulin-tolerance Tests

	Blood Sugar in mg./100 ml. at Minutes											K	Comments
	0	10	20	30	40	50	60	70	80	90	120		
100 g. glucose orally:													
Antony, normal state	80 (3·9)			84			90			68	76 (3·7)		Increased glucose tolerance
Susan, ,, ,,	76 (4·0)			88			94			82	80 (2·7)		,, ,, ,,
25 g. glucose i.v.:													
Antony, paralysed ..	120 (3·0)	213	239	195	159 (2·5)	141	109	96	104 (2·7)			4·9	Normal disappearance rate
,, ,,	98 (3·0)	198	194 (3·1)	153	140	125	98	90	98 (3·0)			3·8	,, ,, ,,
,, post-paralysis	21 (3·8)	215	185	165 (3·6)	145	119	128	102	94	78 (4·1)		1·4	Low disappearance rate
,, ,, ..	76 (4·4)	164	162	144	126	118	120	103	96 (3·6)			2·1	,, ,, ,,
Susan, normal state ..	91 (4·1)	292	270	175	150	129	92	92	63 (3·9)			5·7	Increased disappearance rate
,, paralysed ..	68 (2·5)	243	192	175	150	112	94	72	64 (2·7)			4·1	Normal ,, ,,
,, post-paralysis ..	87 (4·1)	280	250	207	191	166	146	120 (3·8)				2·3	Low ,, ,,
6 units soluble insulin i.v.:													
Antony, normal state	68 (3·6)	47		7	22		16	22		33	55 (2·4)		Hypoglycaemia unresponsiveness
,, paralysed ..	48 (3·1)	51	34	8		21	54		50	52	65 (2·6)		Normal response
5 units soluble insulin i.v.:													
Susan, normal state	67 (3·9)	50	8	6		25	41	46		55 (3·4)	54		Hypoglycaemia unresponsiveness
,, paralysed	91 (2·7)	100	74	65		52	35	17 (2·5)		22	35		,, ,,

Figures in parentheses are serum potassium values in mEq/l. K = glucose disappearance rate in %/minute.

diabetic curves and 70 g. of glucose a normal response. On all these occasions marked paralysis and a profound fall in the serum potassium level occurred. Intravenous glucose-tolerance tests revealed a rapid disappearance rate between attacks, a normal rate during an attack, and a low rate immediately after an attack. Hypoglycaemia unresponsiveness was demonstrated between and also during attacks of paralysis.

Serum Potassium

During precipitated and spontaneous attacks of paralysis the characteristic fall in the serum potassium was observed. The lowest levels recorded were 1.8 and 2.1 mEq/l. Although there was a tendency for the serum potassium level to reflect the severity of paralysis the relationship was not exact.

The changes observed during intravenous glucose-tolerance tests were within normal limits. During the two insulin-sensitivity tests performed with the patients in the normal state the serum potassium fell rapidly to 2.6 and 2.7 mEq/l., with a total fall of over 1 mEq/l. On each of these occasions hypoglycaemia unresponsiveness was observed. On neither occasion was an attack precipitated, although on one occasion a tendency might have been masked by 4 g. of potassium chloride which was given at the end of the test. This response was compared with that of five normal controls (aged 19–27). The lowest serum potassium level recorded in these subjects was 3.5 mEq/l., and on no occasion was the total fall more than 0.9 mEq/l.

The Electrocardiogram

Antony's E.C.G., taken in the normal state, showed tall peaked T waves resembling those seen with hyperkalaemia. The R and S waves suggested slight left ventricular hypertrophy. Susan's E.C.G. in the normal state was normal. During attacks the usual features associated with hypokalaemia were observed. Flattening of the T wave was the earliest change, but inversion did not occur until the serum potassium level fell below 2.4 mEq/l. On many occasions the E.C.G. showed marked changes before a significant fall in the serum potassium occurred, persisting for up to two hours after the serum potassium had returned to normal levels. This was especially seen after intrajejunal glucose and intravenous insulin. Compared with normal controls intravenous insulin caused a more rapid and profound change in the E.C.G., correlating with the greater fall in serum potassium levels, and a delayed return to normal after the restoration of a normal serum level.

The changes in the E.C.G. suggest that membrane potential changes occur before the serum potassium changes and persist after it is restored to normal.

Creatine and Creatinine Excretion

Each twin showed a persistent creatinuria of 300–900 mg. daily with a creatinine excretion of 500–1,000 mg. daily. Serial estimations each 12 hours for five weeks were performed for Susan. On one occasion the 12-hour creatine excretion dropped from over 200 mg. before the attack to under 80 mg. for 36 hours during and after the attack. On four other occasions no significant change occurred in relation to an attack.

Studies on Father and Peter

Limited studies were carried out on these members. Each showed hypoglycaemia unresponsiveness to intravenous insulin but a normal response to intravenous glucose. The father, during the insulin-sensitivity test, showed a fall in serum potassium from 4.2 to 2.7 mEq/l., with the production of moderate weakness of the arms and legs. Peter, although not weak, showed a resting serum potassium level of 3.2 mEq/l., which fell to 2.3 mEq/l. during the insulin sensitivity test. He was able to walk away apparently unaffected at the conclusion of this test.

The father showed a creatinuria of 286 and 323 mg./day. The creatinine output was 1,040 and 1,240 mg./day. Peter showed a creatinuria of 126 and 283 mg./day, with a creatinine output of 723 and 564 mg./day.

Results of Balance Studies (Susan)

On a daily sodium intake of 126 mEq, sodium retention of 50–60 mEq/l. in 24 hours occurred on three occasions. On two occasions 100 g. of glucose was given during this period of sodium retention. On each occasion a severe attack of paralysis resulted with a fall in the serum potassium level. On the occasion when glucose was not given paralysis did not occur, nor did the serum potassium fall (Fig. 2). Sodium diuresis followed the retention irrespective of whether or not paralysis had occurred. On a restricted sodium intake (22 mEq/l./day) a severe attack of paralysis was precipitated by 150 g. of glucose in two doses when minimal sodium retention (less than 10 mEq/l.) was occurring (Fig. 3).

On the restricted sodium intake minor attacks were not reduced in frequency nor was there any clinically demonstrable improvement in muscle strength.

After 14 days on this regime the aldosterone antagonist spironolactone in a dose of 200 mg. twice daily was given. This produced an immediate increase in sodium excretion with a negative sodium balance of 100 mEq in six days. Minor attacks were frequent during this period. After seven days' treatment with spironolactone the patient complained of headache and muscle aches which were thought to be due to sodium depletion. 100 g. of glucose given at this stage again produced a major attack of paralysis with only slight preceding sodium retention (Fig. 4).

It appeared that a change in sodium balance in either direction resulted in an increased incidence of minor attacks manifested by weakness and loss of reflexes. Serum potassium levels rarely fell below 3.5 mEq/l. during these attacks.

Potassium excretion fell during major attacks in parallel with the fall in serum levels. Minor attacks were usually, but not invariably, accompanied by a fall in urinary potassium excretion. On these occasions a close parallel between the degree of potassium retention and the serum potassium level was observed.

No significant changes in the serum sodium level were observed at any time.

Discussion

The almost invariable occurrence of paralysis in these patients after the ingestion of moderate amounts of glucose directs attention to the possibility of altered carbohydrate metabolism. Increased peripheral uptake of glucose as suggested by MacGregor and Shaper (1957) is confirmed by hypoglycaemia unresponsiveness and by flat oral glucose-tolerance curves in the presence of efficient intestinal absorption of glucose. Studies of peripheral uptake, using the intravenous glucose-tolerance test, indicate that this varies between wide limits. Because of the frequency and duration of severe attacks it was often not possible to be sure whether glucose

tolerance was being tested in a pre- or a post-attack phase. However, although not conclusive, our results are consistent, in each case, with the suggestion that after an attack of paralysis the peripheral uptake of glucose is reduced, due either to exhaustion of the membrane carrier mechanism or to saturation of intracellular storage mechanisms. Increased peripheral uptake was found on the only occasion when this was tested with the patient (Susan) in an unequivocally normal state.

The findings after intrajejunal glucose and intravenous insulin suggest that rapid peripheral uptake of glucose precedes the fall in serum potassium and is responsible, at least in part, for this. The changes in the E.C.G. suggest that, in cardiac muscle at least, the membrane potential changes before the serum potassium falls, and this is likely to be due to intracellular binding of potassium, probably to glycogen. Studies in the yeast cell (Pulver and Verzár, 1940), the human erythrocyte (Harris, 1941), and the liver (Fenn, 1939) have previously demonstrated the close relationship of potassium and glucose and glycogen metabolism.

The fact that skeletal muscle plays a dominant part in the uptake of potassium in patients with periodic paralysis has been shown by Jantz (1947), using serial muscle biopsy, Zierler and Andres (1956), and Grob *et al.* (1957). The last-mentioned workers also demonstrated a greater fall in venous potassium levels after glucose and insulin in these patients than in normal controls. This observation has been confirmed in our cases.

The mechanism of paralysis is still not clear. Several factors may be involved. Grob *et al.* believed it to be consequent on hyperpolarization of the cell membrane due to an increase in the ratio of intracellular to extracellular potassium. It is likely that much of the excess intracellular potassium is bound to glycogen, although Denny-Brown (1953) suggested abnormal binding of potassium to muscle protein as an early event in the production of paralysis.

Potassium has been shown to be essential for the production of adenosine triphosphate (A.T.P.) (Boyer *et al.*, 1943); and Beccuau *et al.* (1955) found that paralysis in this condition was relieved by the administration of this substance. The high energy bonds of A.T.P. are believed to be the immediate source of energy for muscle contraction, and a deficiency of these bonds is a possible factor contributing to paralysis.

Persistent creatinuria and diminished creatinine excretion was similar in degree to that observed by Talbott (1941). Abnormalities in creatine and creatinine excretion have long been recognized in periodic paralysis. These findings indicate that creatine metabolism in muscle is decreased. This is consistent with the observation of Brand and Harris (1932) of diminished creatine and, to a less extent, phosphocreatine content of muscle in a patient with periodic paralysis. Since the main function of creatine is that of a storage mechanism for high-energy phosphate bonds as phosphocreatine, it is possible that these cases lack the normal reserve of these bonds.

This possibility is of interest in view of the investigations of Randle and Smith (1958), who found that anaerobiosis and substances which inhibit oxidative phosphorylation accelerate the entry of glucose into the cells of the rat diaphragm. They concluded that the entry of glucose into cells was restrained under basal conditions by a process dependent on a supply of high-energy phosphate. The finding of an increased uptake of glucose by ascitic tumour cells due to a lack of mitochondrial A.T.P. (Wu and Racker, 1957) is consistent with this conclusion.

In view of these observations it is possible that a basic abnormality in periodic paralysis is a deficiency of high-energy phosphate bonds in the muscle cells, probably related to an inability to store creatine. This would lead to increased uptake of glucose, intracellular deposition of glycogen, a fall in serum potassium, and hyperpolarization of the cell membrane. As well as this there is a deficiency of the immediate source of energy required

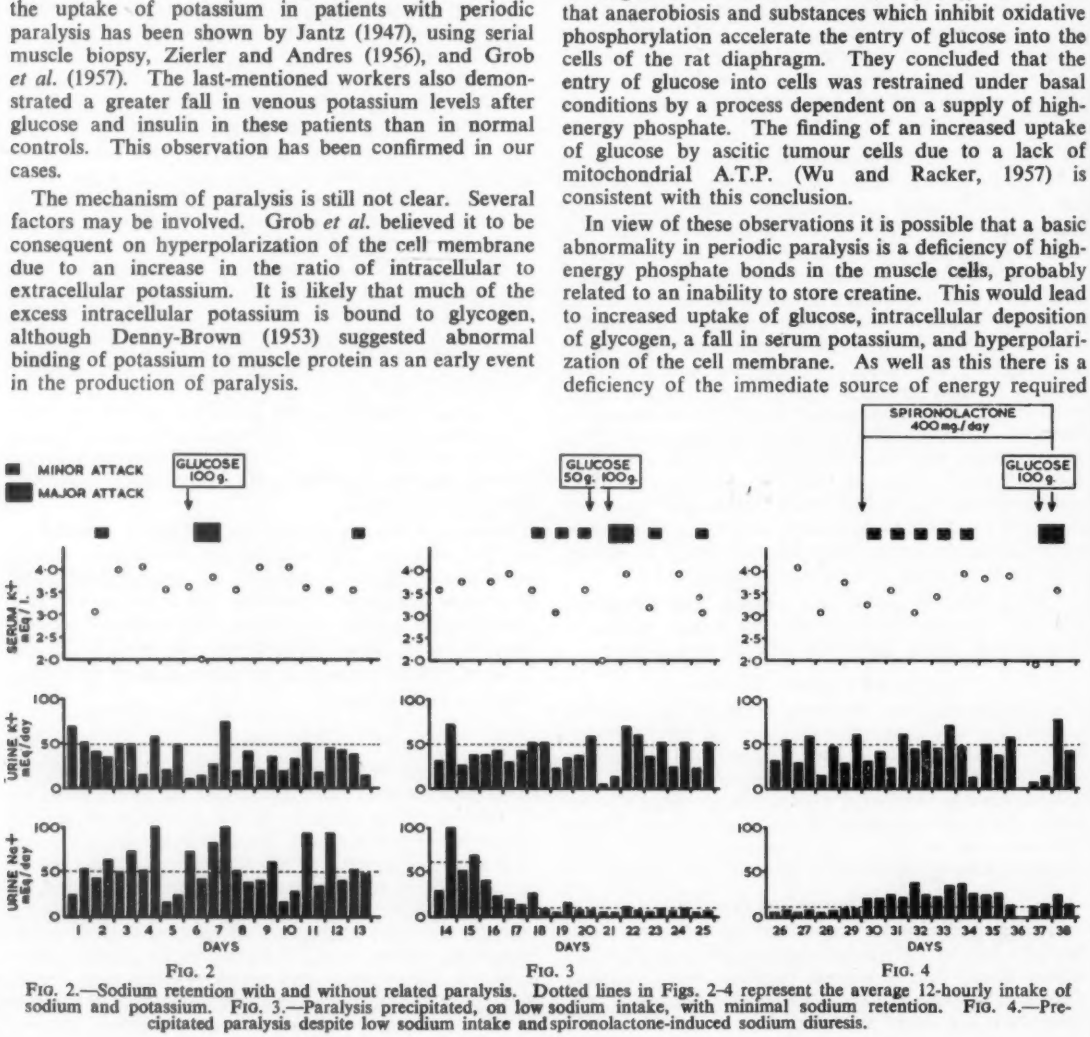

FIG. 2 FIG. 3 FIG. 4

FIG. 2.—Sodium retention with and without related paralysis. Dotted lines in Figs. 2-4 represent the average 12-hourly intake of sodium and potassium. FIG. 3.—Paralysis precipitated, on low sodium intake, with minimal sodium retention. FIG. 4.—Precipitated paralysis despite low sodium intake and spironolactone-induced sodium diuresis.

for muscle contraction. The intermittent nature of the paralysis and the variability in glucose tolerance demonstrated in our cases, in particular the decreased tolerance after paralysis, is not well explained. However, the latter observation is likely to be due either to exhaustion of a carrier mechanism in the cell membrane or to saturation of intracellular storage of glycogen.

The well-recognized association of periodic paralysis with thyrotoxicosis might be related to the ability of the thyroid hormone to uncouple oxidative phosphorylation.

Since Conn *et al.* (1956) demonstrated that sodium retention was important in the precipitation of attacks of periodic paralysis and that treatment with a low-salt diet after preliminary desalting was effective in preventing attacks, a number of balance studies in patients with periodic paralysis have been reported. Although all studies have confirmed sodium retention in relation to some attacks, sodium retention does not appear to be an essential accompaniment to paralysis (Jones *et al.*, 1959). The finding of only minimal sodium retention, during sodium restriction, in our patient in relation to a severe attack of paralysis supports this. The observation, together with the finding of marked sodium retention without the production of paralysis, suggests that sodium retention is not the primary defect in this condition. The discovery of sodium retention after glucose and insulin administration (Conn *et al.*, 1957) suggests a possible relationship between the abnormalities in sodium and carbohydrate metabolism. The mechanism of this association and the initial trigger to the chain of events leading to paralysis have yet to be determined. However, since the extrusion of sodium from the cell is an active process requiring energy (Hodgkin, 1958), it is possible that a transient reduction in the available high-energy bonds would lead to sodium retention by the cell. This would provide a common cause for sodium retention and the rapid peripheral uptake of glucose.

The failure, in our case, of a daily sodium intake of 22 mEq and diuretic agents to prevent attacks is similar to that described by Eales *et al.* (1958), although in their case such treatment initially appeared effective. More rigid sodium restriction to 8 mEq daily as used by Conn might be more effective, but from the practical therapeutic aspect such treatment seems to have little to offer.

Summary

Glucose and insulin tolerance were studied in four members of a family, including non-identical twins, affected with periodic paralysis. Evidence was obtained indicating rapid peripheral uptake of glucose as a regular finding in these patients. With the use of the intravenous glucose-tolerance test, the glucose disappearance rate was variable, being rapid before paralysis and reduced after.

In the one case specifically studied sodium retention and paralysis at times occurred independently of each other.

It is suggested that there is a lack of high-energy phosphate in the muscle cells, related to an inability to store creatine, leading to increased glucose uptake. A similar mechanism may be responsible for intracellular sodium retention.

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NUTRITIVE VALUE OF BREAD MADE FROM FLOUR TREATED WITH CHLORINE DIOXIDE

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The rejection of agene, NCl_3, as a flour improver, which followed the finding that flour so treated causes hysteria in dogs (Mellanby, 1946), raised in the milling and baking industries the problem of finding a suitable substitute. In the U.S.A. and Canada chlorine dioxide was used to replace agene from 1950 onwards (Horder, Dodds, and Moran, 1954), and later this substance came into general use in this country. For the formation of methionine sulphoximine, the poison responsible for canine hysteria, the nitrogen atom of agene must combine with methionine present in flour (Bentley, McDermott, Moran, Pace, and Whitehead, 1950). On theoretical grounds, therefore, it is clear that chlorine dioxide could not produce this particular poison. In agreement with this conclusion, experiments in the U.S.A. by Newell, Gershoff, Suckle, Gilson, Erickson, and Elvehjem (1949) demonstrated that dogs remain free from hysteria when given flour heavily treated with chlorine dioxide for 13 weeks. Rats, rabbits, and monkeys also remained well when given the treated flour for periods of 5, 6, and 22 weeks respectively. In human subjects no evidence of poisoning could be found after they had received diets containing flour treated with chlorine dioxide at 80 p.p.m., and wheat gluten treated

with 400 p.p.m., for six weeks. For the commercial treatment of white flour in Britain the level of addition of chlorine dioxide is at present only 15–20 p.p.m.

Although chlorine dioxide does not cause the formation of methionine sulphoximine in flour, and although there is no evidence of the formation of any other highly toxic substance, the flour does not escape injury. Thus it has been clearly proved, by both chemical and biological methods, that even treatment with chlorine dioxide at about the ordinary commercial level causes almost complete destruction of the vitamin E which is naturally present in the flour (Moran, Pace, and McDermott, 1953, 1954; Frazer, Hickman, Sammons, and Sharratt, 1956a; Moore, Sharman, and Ward, 1957, 1958). Another indication of injury to the flour, apparently distinct from the destruction of vitamin E, may perhaps be seen in the results of feeding-trials with successive generations of rats by Frazer, Hickman, Sammons, and Sharratt (1956b). These workers observed that mean growth rates were always slower when the diet contained flour heavily treated with chlorine dioxide than when the flour was lightly treated. Between some groups, however, the differences were not statistically significant, and the authors' own conclusion was that even the heavily treated flour had no deleterious effect on rats.

The purpose of this paper is to report further evidence that the treatment of flour with chlorine dioxide causes reduced growth rates in multi-generation experiments with rats, even when doses of vitamin E are given to compensate for its destruction by the improver.

Diet

The experiments to be described were carried out during 1952–4, and the flour used was of the 80% extraction rate then current. Repeated batches of flour were necessary, but the quality was kept as uniform as possible. Some of the flour was left untreated, and was used for baking 2–10 weeks after milling. Treatment of the flour with chlorine dioxide was carried out weekly at the Cereals Research Station, St. Albans, and the flour was then sent, together with untreated flour, to the Baking Industries Research Station, Chorley Wood, for baking. Two levels of treatment with chlorine dioxide were chosen—30 p.p.m. (normal) and 300 p.p.m. (normal × 10). After baking, the bread was sliced, dried under gentle heat in a current of air, and ground to fine crumbs. The reason for this otherwise undesirable treatment was to allow for the mixture of the bread with other dietary components. The diet was composed as follows:

	Parts by weight
Dried breadcrumbs	80
Casein	8
Arachis oil	12
Salt mixture	5
Dried yeast	7

Each rat was dosed weekly with about 1,000 I.U. of vitamin A and 40 I.U. of vitamin D, supplied as one drop of halibut-liver oil. Vitamin E was supplied as 2 mg. of DL-α-tocopheryl acetate weekly, dissolved in two drops of arachis oil. Vitamin K was supplied as 0.05 mg. of 2-methyl-1:4-naphthoquinone weekly, dissolved in one drop of arachis oil.

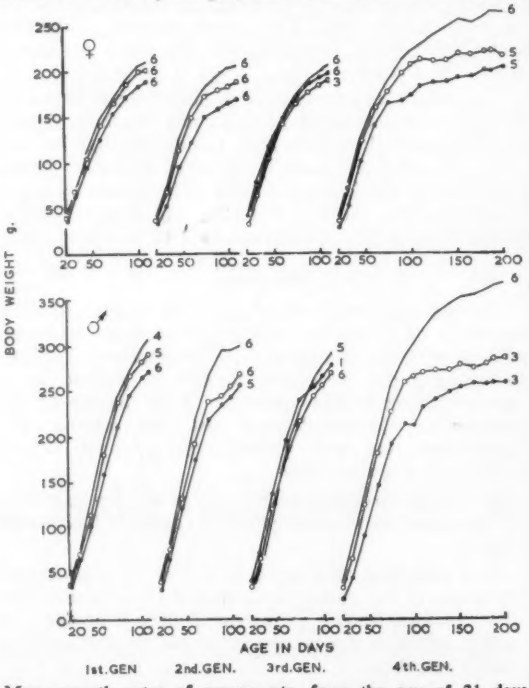
Preliminary Experiments with Weanling Rats

When groups of weanling rats, whose mothers had received a good mixed diet, were fed upon the diet containing breadcrumbs their mean rates of growth, over a period of 200 days, were virtually identical irrespective of whether the flour had been untreated or treated with chlorine dioxide at the N or N × 10 levels. In all the groups given diets containing breadcrumbs, however, growth was much slower than in rats given a good mixed diet. Hutchinson, Moran, and Pace (1956) found that supplements of lysine increase the growth rate in young rats fed upon bread. The inclusion in our diet of 8% of casein, however, makes it doubtful whether lysine was the limiting factor in our experiments.

Multi-generation Experiments

These trials were started by mating adult male and female rats which had previously been used successfully for routine breeding purposes. At mating, the experimental diets, containing breadcrumbs, were substituted for the previous mixed diets. For each experimental diet four pairs of rats were used. From their young six males and six females were taken at weaning, being selected to include the best available, subject to representatives being taken from each litter. The selected groups of males and females were kept on the same experimental diets for 110 days. Four males and four females were then taken from each group and mated. The procedure of taking six males and six female rats at weaning for growth trials, and later restricting them to four pairs for breeding another generation, was then repeated. In this way four generations of offspring were bred. In the final generation the growth trials were extended beyond the usual period, which was possible because no rats had to be taken for mating.

The mean growth curves of the rats, as indicated by increases in body weight, are shown in the Chart. It



Mean growth rates of young rats, from the age of 21 days onwards, in four generations reared upon diets containing breadcrumbs made from (1) untreated flour (plain lines), (2) chlorine dioxide at 30 p.p.m. (white circles), or (3) chlorine dioxide at 300 p.p.m. (black circles). The number of rats in each group is shown at the end of each curve.

will be seen that in both males and females growth was always somewhat more rapid when the breadcrumbs had been made from untreated flour than when the flour had been treated with chlorine dioxide. Comparisons between the groups given crumbs from N or N × 10 treated flours usually indicated more rapid growth with the lighter treatment. In generation 3, however, growth was more rapid with the N × 10 treatment than with N treatment for both males and females. This unexpected result coincided with failures in reproduction or lactation in generation 2, which prevented the full groups of six rats each being set up in generation 3. Thus only one male was available for the ClO_2 N × 10 group, and only three females for the ClO_2 N group. No significance can therefore be attached to this change from the usual relationship.

In addition to the gaps in groups caused by failures in breeding, two rats died during the period of their growth trials. These were a male in the 2nd generation in the ClO_2 N × 10 group, and another male in the 3rd generation in the "untreated" group. It seems unlikely that these deaths were related to the nature of the diet. In plotting growth curves, and in statistical calculations, observations on both these rats have been excluded.

For statistical treatment the weight increases observed between the ages of 21 and 110 days for all four generations were combined according to sex and the treatment of the flour. From Table I it will be seen that in both sexes growth was most rapid in those rats which received breadcrumbs made from untreated flour. Growth was slower in the rats given crumbs which had received the N level of treatment with chlorine dioxide, and slower still with the N × 10 treatment. In all instances the differences between the untreated groups and the chlorine dioxide N or N × 10 groups were statistically significant.

In the experiments of Frazer *et al.* (1956a, 1956b) the young of rats from mothers fed upon flour treated with chlorine dioxide at the N × 10 level tended to be lighter, at an age of 14 days, than the young of mothers given flour treated at the N level. We have therefore compared the weights of our young rats at the age of 21 days, when they were weighed for the first time. From Table II it will be seen that our results were in agreement with those of Frazer *et al.* regarding the relative weights of the young in the chlorine dioxide N and N × 10 groups. For statistical purposes, however, it seemed more informative to make comparisons with the "untreated" group rather than between the two chlorine dioxide groups. Presumably this was not done in the investigation of Frazer *et al.* because the trials with untreated flour were discontinued after only two generations. It will be seen that in our experiments the differences between the weights in the young in the chlorine dioxide groups, with one exception, were significantly different from those in the untreated groups. The exception was for females in the chlorine dioxide N group.

TABLE I.—*Growth, as Indicated by Weight Increases, in Rats Fed Upon Diets Containing Breadcrumbs Made From Untreated Flour, or from Flour Treated with Chlorine Dioxide at a Normal (30 p.p.m.), or at 10 Times the Normal, Level (300 p.p.m.). Combined Results for Four Generations*

	Treatment of Flour	No. of Rats	Mean Weight Increase (g.) between Ages 21 and 110 Days	P ClO_2/Untreated
Males	Untreated	21	264	
	ClO_2 N	21	239	<0·001
	ClO_2 N × 10	14	226	<0·001
Females	Untreated	24	174	
	ClO_2 N	23	161	0·05–0·01
	ClO_2 N × 10	20	147	<0·001

TABLE II.—*Body Weights of Weanling Rats, Aged 21 Days, Reared by Mothers Fed Upon Diets Containing Breadcrumbs Made From Untreated Flour, or From Flour Treated with Chlorine Dioxide at N or N × 10 Levels. Combined Results for Four Generations*

	Treatment of Flour	No. of Rats	Mean Weight (g.) at Age of 21 Days	P ClO_2/Untreated
Males	Untreated	21	39·4	
	ClO_2 N	21	35·7	0·001<P<0·01
	ClO_2 N × 10	14	32·1	<0·001
Females	Untreated	24	37·4	
	ClO_2 N	23	35·5	0·1<P<0·2
	ClO_2 N × 10	20	32·8	0·001<P<0·01

Palatability

In experiments in which rats have been allowed a choice between various diets Moran, Pace, and Hutchinson (1955) have shown that diets containing fat extracted from untreated flour are preferred to diets containing fat from flour which has been heavily treated with agene or chlorine dioxide. These workers, and also Frazer *et al.* (1956b), have suggested that reduced palatability, leading to a decrease in food intake, may be an important factor in the interpretation of data on growth rates.

Undue emphasis of this factor seems hazardous, in the first place, because Moran *et al.* found that their rats usually had good appetites for a diet which was their second choice if their first choice was not available. Secondly, lowered food intakes may well be expected in rats which are growing slowly as the result of impairment in the nutritive value of their food. If we ascribe reduced growth rates to decreased palatability, without proof that this is the true and only explanation, we may defeat the purpose for which our feeding trials have been carried out.

In the present investigation the slower growth rates in the rats given breadcrumbs made from flour treated with chlorine dioxide, at least at the N × 10 level, was not due to reduced palatability. In experiments extending over eight weeks six young male rats were offered a choice between the chlorine dioxide N × 10 diet and the untreated diet. Food intakes of each diet were recorded daily. Table III shows the mean daily intakes of food for each rat in successive weeks. It will be seen that the diet treated with chlorine dioxide was consistently preferred to the untreated diet. Thus five of the six rats ate much more of the treated diet than of the untreated, and the sixth rat slightly more. An interesting point was the decided preference of all the rats for the treated diet in the first two weeks of the experiments. This suggests that they found the treated diet more "palatable." In later weeks larger amounts of the untreated diet were eaten, and in a few instances the mean weekly consumptions of untreated diet temporarily exceeded those of treated diet. This tendency seems in agreement with the findings of Harris, Clay, Hargreaves, and Ward (1933) that in some circumstances rats may learn by experience to discriminate between nutritionally adequate and inadequate diets.

Discussion

If we first restrict our attention to the difference between growth rates in successive generations of rats

TABLE III.—*Average Daily Food Intakes of Rats Given a Choice Between a Diet Containing Breadcrumbs Made from Untreated Flour or from Flour Treated with Chlorine Dioxide* (N×10)

Days on Experiment	Mean Daily Intakes (g.) of Each Diet													
	Rat 1		Rat 2		Rat 3		Rat 4		Rat 5		Rat 6		Means	
	Untr.	ClO_2	Untr.	ClO_2	Untr.	ClO_2	Untr.	ClO_2	Untr.	ClO_2	Untr.	ClO_2	Untr.	ClO_2
0–7	1·8	7·6	1·7	9·0	0	7·0	1·3	7·3	0·3	8·8	2·6	6·8	1·3	7·8
8–14	2·3	10·3	3·6	9·0	1·6	8·4	2·8	7·4	1·7	9·8	4·5	6·3	2·8	8·5
15–21	4·2	9·7	7·0	7·7	7·2	4·9	4·7	6·8	5·2	7·9	6·4	6·2	5·8	7·2
22–28	4·0	10·3	8·0	7·8	9·1	5·5	5·1	8·3	6·1	8·9	8·2	6·1	6·8	7·8
29–35	3·5	12·6	7·6	8·7	6·5	9·6	6·1	8·6	7·6	7·4	9·0	6·0	6·7	8·8
36–42	3·0	14·0	6·8	10·5	7·7	8·5	5·9	8·9	5·8	9·4	7·0	7·7	6·0	9·8
43–49	3·6	14·1	5·9	11·6	5·1	12·7	7·1	8·3	9·6	6·5	6·4	8·7	6·3	10·3
50–56	4·2	12·5	6·4	11·0	5·1	11·4	6·0	10·0	8·9	7·6	7·2	7·5	6·3	10·0
Means	3·3	11·1	5·9	9·4	5·3	8·6	4·9	8·2	5·7	8·3	6·4	6·9	5·3	8·8

Statistical comparison of the set of six means for the intakes of diet containing breadcrumbs made from untreated flour with the corresponding means for treated flour gave $P<0.001$—that is, a highly significant difference

given crumbs from flours treated with chlorine dioxide at the N and N × 10 levels we find that our results are in good agreement with those of Frazer *et al.* (1956b). Thus growth was slower with the heavy than with the light treatment. Our results also agreed with the finding of Frazer *et al.* that suckling or weanling rats were smaller with the light treatment of the flour than with heavy treatment. Interest in these points of agreement may be increased by the different diets which were used by Frazer *et al.* and by ourselves. Thus in place of dried crumbs Frazer *et al.* included uncooked flour in their diets. Whereas our rats were specially dosed with vitamin E those of Frazer apparently received this vitamin in the dried milk and fish meal which were included in their diet. The retarding effect of heavy treatment with chlorine dioxide on growth, therefore, is not confined to generations of rats receiving one particular type of diet.

Our experiments differed from those of Frazer in the continuation of the breeding of control rats, given breadcrumbs made from untreated flour, throughout the whole course of the investigation. As we have seen, both the growth rates, averaged to include all generations, and the weights at weaning, for our three breeding groups, were in the order (1) untreated, (2) chlorine dioxide N, and (3) chlorine dioxide N × 10. Similar results were obtained for both sexes.

In view of the known destruction of vitamin E in flour by chlorine dioxide, and of the possibility that the diets containing treated flour adversely affected reproduction or lactation, suspicion may be raised that our weekly dose of 2 mg. of DL-α-tocopheryl acetate was inadequate fully to supply the requirements of the rats. Against this possibility we may state that (1) the dosage of α-tocopherol was about five times greater than the minimum which we have found necessary to prevent all signs of vitamin E deficiency in the rat; (2) the weekly dose of α-tocopherol greatly exceeded in vitamin E potency the amounts of tocopherols which could have been derived from untreated flour in the same period; and (3) no signs of vitamin-E deficiency were ever observed in those of our rats which were eventually examined at necropsy, or in many rats similarly dosed and used for other experiments on flour improvers. It remains possible, however, that small amounts of vitamin E evenly distributed throughout the diet, as opposed to being given as a single massive dose, may have some nutritional virtue which is not yet appreciated. The destruction of some factor other than vitamin E, or the formation in the diet of a substance which adversely affects the nutrition of the rat, seems a more probable explanation.

Summary

Successive generations of rats were reared upon diets which consisted mainly of dried breadcrumbs. The bread was made from untreated flour, or from flour which had been treated lightly (30 p.p.m.) or heavily (300 p.p.m.) with chlorine dioxide.

Differences in the mean growth rates of the young rats were observed according to the treatment of the flour. For both sexes the growth was most rapid when the flour was untreated, somewhat slower when the flour had been lightly treated with chlorine dioxide, and slower still when the flour had been heavily treated. The weights of the young rats at weaning were in the same order in relation to the treatment of the flour.

In these experiments all the rats received adequate doses of DL-α-tocopheryl acetate. The slower growth rates when the flour had been treated with chlorine dioxide cannot therefore be explained by the known destruction of vitamin E by chlorine dioxide.

Experiments in which rats were allowed to choose between diets containing breadcrumbs made from untreated flour or from flour which had been heavily treated with chlorine dioxide indicated that the improver increased, rather than decreased, the "palatability" of the breadcrumbs to the rat.

Our thanks are due to Dr. T. Moran, Dr. J. Pace, and the staff of the Cereals Research Station of the Research Association of British Flour Millers for providing specimens of untreated and treated flour. Bread was baked through the kindness of Dr. J. B. M. Coppock, Mr. J. J. Devlin, and the staff of the Baking Industries Research Station. Dr. I. M. Sharman and Mr. K. C. Day helped with the statistical calculations. Finally, we thank our director, Dr. L. J. Harris, for his interest in the work.

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CASE OF LIPOID PROTEINOSIS

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Lipoid proteinosis (Urbach–Wiethe disease; hyalinosis cutis et mucosae) is a rare and striking disorder in which there is a peculiar infiltration of the skin and mucous membrane. Siebenmann (1908) described a case of "ichthyosiform disease" in a 19-year-old girl under the subtitle of "hyperkeratosis cutis universalis, keratosis oris, linguae, labiorum, palati duri et mollis, arcuum et tonsill. pal. epiglottidis et laryngis." His was probably the first clinical description of lipoid proteinosis. Between 1924 and 1929, Urbach and Wiethe (1929) collected nine cases occurring in four families and established this condition as a clinical entity.

Lipoid proteinosis affects the sexes equally, and is often familial, particularly if there is consanguinity. A "diabetic tendency" in the patient and a family history of diabetes mellitus have been reported. These patients usually give a history of hoarseness dating from infancy; the associated laryngeal changes are often progressive and may necessitate tracheostomy. Skin changes, in various forms, appear constantly by the age of 12 years. The scalp shows diffuse non-scarring alopecia. Nodular lesions occur on the lid margins; on the face, where they may lead to pock marks; and on the elbows and knees, where they may progress to form warty hyperkeratotic plaques. There are infiltrated plaques at the angles of the mouth and in the gluteal cleft, which may become deeply fissured and infected. Mauve atrophic patches may be found on the face; and perifollicular atrophy of the neck and upper arms produces an appearance reminiscent of pseudoxanthoma elasticum. Attacks of stomatitis and parotid swelling are described. Similar changes involve the mucous membranes of the nose, mouth, pharynx and larynx, and the vagina and anal canal. Any of the above features may be absent.

The clinical aspects, pathological findings, and literature have been well reviewed recently (Laymon and Hill, 1957; Eberhartinger and Niebauer, 1959; Ungar and Katzenellenbogen, 1957). Ramos e Silva (1943) described two additional features found in this condition—petechiae of the face and endocranial calcification, which he thought occurred in dural folds. By 1959 endocranial calcification had been found in 8 out of 18 patients with lipoid proteinosis in whom *x*-ray examination of the skull had been carried out, and two of these suffered from epilepsy. Eberhartinger and Niebauer thought that the calcification in their two patients was in the brain substance. Since then eight further cases of endocranial calcification have been described—four "above the pituitary fossa," three "in the hippocampus," and one "in the temporal lobes" (Scott and Findlay, 1960). No epilepsy, however, was noted by these authors.

About 100 cases of lipoid proteinosis have now been reported, but we believe the following case to be the first in Great Britain. This case is of special interest in that intermittent bruising, with a strongly positive tourniquet test, was present. The histological findings indicate that there are grounds for believing that increased capillary fragility plays an important part in the pathogenesis of this condition.

Case Report

A 42-year-old housewife was first seen in the skin department in June, 1958, having been referred by the E.N.T. surgeons. Her appearance was striking—a tall, thin, pale woman with sparse hair and a "plucked chicken" appearance of the skin of the neck. She talked in a hoarse whisper. Known to be an epileptic, she was taking phenytoin sodium. A provisional diagnosis of pseudoxanthoma elasticum was made, although no angioid streaks of the retina were seen. The diagnosis of lipoid proteinosis was suggested on histological grounds by Dr. A. H. T. Robb-Smith.

On re-examination it became obvious that hers was a classical example of this condition. It began in infancy, when she always cried silently, and even when red in the face with rage she seemed unable to make a noise. At the age of 12 years she developed a lesion on her left shoulder, diagnosed as a "ringworm," which has remained, leaving a heaped-up scarred area. At the same time she noticed the beginning of skin changes of the neck. She was quite sure that at the age of 10 years her skin was normal, and that by the age of 12 it had its present appearance. In her thirties she developed "blackouts" and was diagnosed as having akinetic epilepsy by Dr. C. W. M. Whitty in 1956. Neurological examination revealed nothing abnormal. An electroencephalographic report stated: "Very low voltage record showing paradoxically some 10 c/s alpha rhythm over the anterior part of the head only. Some 18 c/s low-voltage activity is more diffuse. No change on over-breathing. No sign of epileptic action. Probably normal."

Her epilepsy was well controlled when she took phenytoin ½ gr. (50 mg.) t.d.s. Otherwise she had always been well and had had no serious illnesses. She did, however, suffer from migraine.

Her periods, which began at the age of 14, were scant and irregular until 1956, when they became heavy but regular, and she complained of flooding. This was regarded by the gynaecologists as "dysfunctional endocrine bleeding of a mild nature." Dilatation and curettage was refused by the patient, as it could not be guaranteed to be curative. At the same time as the "flooding" she also developed an increased tendency to bruise. She was seen in the ear, nose, and throat department in 1956 by Mr. R. G. Macbeth on account of her hoarseness, and was found to have thickening of the false vocal cords.

She was an only child. Her mother developed diabetes mellitus in middle age, but her father and six aunts and uncles were all well. She had four children, one of whom had flexural eczema. There was no other family history of diabetes mellitus, epilepsy, skin disease, or consanguinity, but her paternal grandmother had been hoarse.

Examination in September, 1958, showed a middle-aged woman with diffuse non-scarring alopecia, most pronounced in the occipital region (Fig. 1), whose hair was brittle and dry. Her face was waxy, deeply wrinkled, and immobile (Fig. 2). On the right side of the forehead she had a slightly atrophic mauve lesion. Her eyebrows were normal, but the eyelashes were scanty, and the upper lid margins were studded with pearly, bead-like lesions. The margins of her nostrils were thickened and she had infiltrated plaques at the corners of the mouth, with fissuring. On the neck, chest, upper arms, and, to a less extent, on the forearms there were yellowish follicular papules with slight perifollicular atrophy. The skin had an "elastic" feel which was

noticed particularly on biopsy. Warty, hyperkeratotic, shiny plaques were present over both elbows, with a small excrescence on the left (Fig. 3). On the left shoulder there was a lesion 1 in. (2.5 cm.) in diameter, pale and wrinkled, with perifollicular atrophy and some infiltration. In the gluteal cleft she had an infiltrated, reddish, puckered lesion. The vulva, vagina, and anus were normal. Widespread bruising was present, and a tourniquet test for capillary fragility was strongly positive.

There was crusting of the vestibules with some stenosis of both nostrils. The nasal mucosa showed moderate atrophic rhinitis. The pharynx and post-nasal space were normal. At indirect laryngoscopy only half the larynx was visible and the patient appeared to phonate with the false vocal cords. Direct laryngoscopy and bronchoscopy by Mr. R. G. Macbeth showed that the posterior halves of both vocal cords were thickened and "knobbly." The tissue in this situation was white in colour. There was some thickening over the arytenoids in the interarytenoid region. The epiglottis, aryepiglottic folds, and subglottic regions were normal. A biopsy was taken. The bronchi appeared normal. General examination was otherwise normal.

FIG. 1

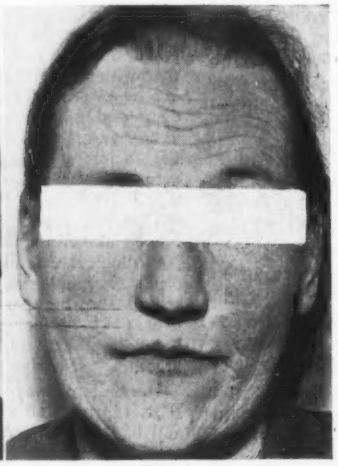

FIG. 2

FIG. 1.—Photograph of patient, showing area of alopecia. FIG. 2.—Face waxy, deeply wrinkled, and immobile.

FIG. 3.—Showing warty hyperkeratotic plaques on elbow.

After diagnosis and further investigation, treatment with prednisolone 5 mg. t.d.s. was begun in September, 1958. One month later her voice was louder, and skin changes were less marked. There was practically no bruising and the tourniquet test was only weakly positive. By January, 1959, the skin had continued to improve and felt less "elastic" and infiltrated; there was no bruising, and a tourniquet test was negative. However, steroid therapy was tapered off in May, 1959, as she was developing rosacea-like pustules. There was little change until July, 1960, when she was found to have non-tender swelling of the left submandibular gland, lasting for one month. She had been a mumps contact. During the last 12 months the voice has deteriorated. She has had increasing dyspnoea, her hair has become sparser, and her skin has remained the same.

A further ear, nose, and throat examination showed an advanced degree of vestibular stenosis on both sides. The pharynx was dry with some reddish discoloration of the soft palate and submucosal infiltration. Indirect laryngoscopy showed considerable thickening of both vocal cords. The larynx was pale, with scarring and some proliferation posteriorly. Some oedema of the arytenoid region was present. The tourniquet test in October was weakly positive. Cineradiographic examination confirmed extensive involvement of the larynx (to be reported later).

Investigations.—Initially, in 1958, the following tests were carried out: haemoglobin, 91% (Haldane); white-cell count 7,600/c.mm. (normal differential count); platelets, 235,000/c.mm.; bleeding-time (Ivy) 4, 5, and 6½ minutes. Capillary microscopy of the skin showed nothing abnormal. The tourniquet test was strongly positive and this was thought to be sufficient to account for the abnormal bruising. The direct Coombs test was negative in all dilutions using three different Coombs reagents. Wassermann and Kahn reactions were negative. Total blood serum proteins were 6.5 g./100 ml. (albumin 4.5 g., globulin 2 g.) and paper electrophoresis showed a normal pattern. Blood cholesterol was 200 mg./100 ml. and blood lipoid phosphorus 5.2 mg./100 ml. Urine examination was normal. These tests have remained normal on repeated examination.

Radiological Examinations

Chest: normal.

Sinuses: "Sinuses appear clear. Bilateral intracranial opacities projected over antra in occipito-mental view—? nature."

Skull (report by Dr. P. W. E. Sheldon): "There are solid calcifications overlying the pituitary fossa in the lateral view, but lying about 2.5 cm. from the midline on either side. These are not like dural calcifications, nor do they resemble carotid calcification. They appear to be free from any bone, and must lie somewhere in the region of the anterior parts of the hippocampi or in the amygdaloid nuclei (Fig. 4). However, I am at a loss to explain their precise nature, at least without air studies." Electroencephalogram in 1960 showed "low-amplitude record with a fair amount of symmetrical 10 c/s alpha rhythm in the post-central region. It remains stable on overbreathing. Normal record."

Histology

Biopsy specimens were taken from a nodular area at the posterior end of a vocal cord and from an infiltrated area of skin. These were fixed in neutral formol-saline, and, since they were small and the diagnosis was not suspected, they were embedded entire in paraffin.

The laryngeal biopsy was covered by rather flattened squamous epithelium without hyperkeratosis. In the stroma were large homogeneous areas, usually with comparatively smooth sides and ragged ends, suggestive of degenerate collagen (Fig. 5). They showed no fibrillar pattern and nuclei were scanty, most of those present being of the endothelium of narrow slit-like capillaries. These hyaline areas were brightly eosinophil and a few lymphocytes lay around their margins. In the adjacent stroma many of the capillaries were surrounded by a narrow sharply defined concentric layer of similar hyaline material immediately outside the endothelium (Fig. 6). The same change affected the media of a few small arterioles and surrounded the duct of a mucous gland, the epithelium of which showed squamous metaplasia. The skin biopsy showed flattening of the epidermis with small widely separated rete pegs. Discrete areas of structureless eosinophil material lay in the dermis similar to those in the larynx. Perivascular hyaline material was also present, and a narrow layer surrounded some of the sweat glands, which showed no atrophic changes. With van Gieson's stain, the hyaline material in both biopsies varied from yellow to the khaki colour which suggests, but is not diagnostic of, amyloid. The results with Congo red and methyl violet were negative for amyloid. Argyrophil fibres were plentiful in the superficial dermis except in the hyaline areas. These were entered by a few fine fibrils, but the dermic reticulin pattern was lost within them. No reticulin was seen in the perivascular or periglandular hyaline material, which appeared to be within the basement membrane.

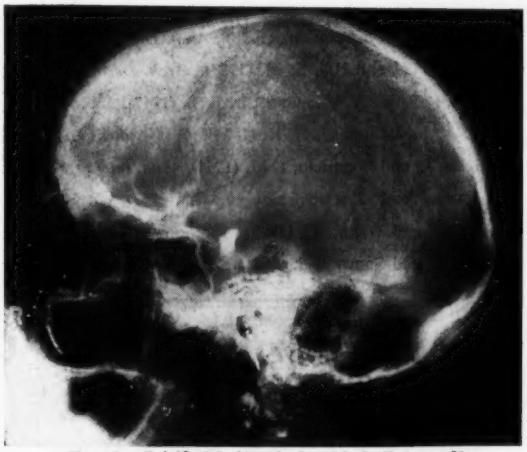

FIG. 4.—Calcified lesions in lateral skull *x*-ray film.

FIG. 5.—Biopsy of vocal cord. (Haematoxylin and eosin. ×100.)

No orcein-positive material was present in some of the hyaline areas. Others contained irregular clumps or short fragments of coarse fibres. Elastica throughout the rest of the laryngeal biopsy was coarse, clumped, and irregular in disposition. The dermic elastica at a distance from the hyaline areas was not strikingly abnormal, but irregularity, clumping, and variation in calibre and staining intensity were prominent in their immediate vicinity. The hyaline material gave a strongly positive periodic-acid/Schiff reaction, unaffected by amylase digestion. Dilute aqueous toluidine blue and thionine both gave a streaky metachromatic reaction. No sudanophil material was preserved in the paraffin sections.

Another biopsy was made of skin taken from a less severely affected area and fixed in Baker's formalin solution with calcium chloride and cadmium chloride. There were small patches of diminution of dermic elastica and others of coarse, clumped, irregular fibres, usually around blood-vessels. Narrow hyaline haloes surrounded some of the capillaries and sweat glands, but no large hyaline areas were present. Frozen sections stained with Sudan black revealed fine lipid droplets localized in zones of degeneration of elastica. Fewer droplets were seen in sections stained with Sudan IV. Baker's acid-haematin method gave a negative result. The melanophores of the superficial dermis contained numerous droplets which stained with Sudan IV and Sudan black, and gave a deep-blue colour with Nile-blue sulphate. Dermic mast cells were very conspicuous in this biopsy, although not so frequent as to be clearly of pathological significance.

Discussion

Most of the classical features of lipoid proteinosis were present in our patient. The following were absent: parental consanguinity, diabetes mellitus in the patient, pock marks on the face, and involvement of the vaginal

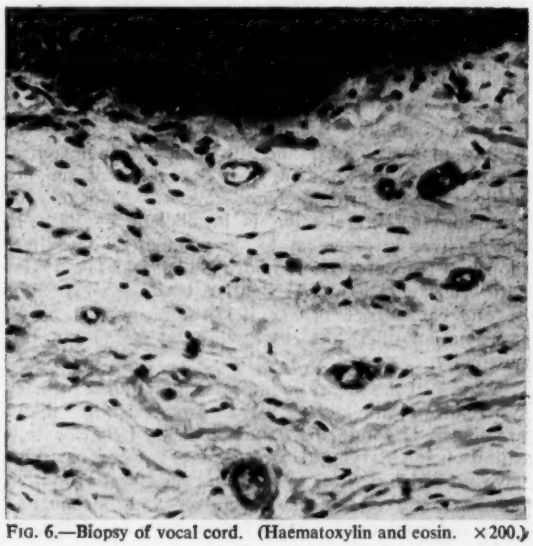

FIG. 6.—Biopsy of vocal cord. (Haematoxylin and eosin. ×200.)

and anal mucosae. She was edentulous at the first visit, and we were unable to find out if she had any dental abnormality, such as has been described by various authors (Gerth and Flegel, 1956). The salivary-gland enlargement, which has previously been described, was unlikely to be mumps, even though she had been a contact, as the clinical course was dissimilar.

Since 1943 endocranial calcification has been noted in some of these patients, and fits, thought to be associated with it, occurred in two cases. The calcification appears to be in the temporal lobes, even in Ramos e Silva's (1943) case. Our patient had bilateral calcification in the temporal lobes, probably medial to the posterior horns of the lateral ventricles; but it was not considered justifiable from the patient's point of view to confirm this by air studies. Her fits were diagnosed as akinetic epilepsy; there was no auditory or gustatory aura as might be expected in temporal-lobe lesions, and electroencephalograms were normal.

The marked bruising tendency with a positive tourniquet test has not previously been described in lipoid proteinosis. It was suppressed completely while she was taking corticosteroids. Probably her menorrhagia was an associated phenomenon. Full investigation of the purpura revealed only increased capillary fragility. This could be explained by the widespread deposition, in and around capillaries, of eosinophilic staining material, rather analogous to primary systematized amyloidosis.

The histological findings leave no doubt that our patient has the same disorder as that described by Laymon and Hill (1957) and by Ungar and Katzenellenbogen (1957), although the changes are less advanced than those described and illustrated in the latter paper. We cannot help to elucidate the nature of the hyaline material, which in its perivascular distribution bears a resemblance to amyloid but in its staining properties shows wide differences. The localization of lipid to the degenerate orcein-positive fibres appears significant, and, so far as they go, our findings seem to support those of Ungar and Katzenellenbogen.

Lipoid proteinosis has been regarded as a systemic disease because of the presence of eye changes (Holtz and Schulze, 1950; Gerth and Flegel, 1956; Scott and Findlay, 1960), association with diabetes mellitus (Urbach and Wiethe, 1929; Tompkins and Weinstein, 1954), testicular involvement (Bazex, 1939), intracranial calcifications and bromsulphthalein retention (Wile and Snow, 1941; Price *et al.*, 1947).

Diabetes mellitus was found only as an associated feature in early cases, and the testicular involvement (Bazex, 1939) took the form of deposition of sudanophilic material around blood-vessels. A degree of bromsulphthalein retention is insufficient by itself to enable liver involvement to be postulated; and liver biopsy of two cases showed normal histology (Tompkins and Weinstein, 1954). Extensive skeletal *x*-ray films of one case (Price *et al.*, 1947) were normal. Full investigation of several cases has not borne out this possibility.

A study of the literature indicates that, unlike primary systematized amyloidosis, the prognosis of lipoid proteinosis is good; the only potentially lethal complication being laryngeal obstruction. Corticosteroids have proved beneficial to skin and laryngeal lesions in our case and one of Eberhartinger and Niebauer's; early and prolonged administration may be of benefit.

Summary

The first British case of lipoid proteinosis of Urbach and Wiethe is described. In addition to the usual features the patient had an increased tendency to bruise, probably caused by infiltration of blood-vessel walls.

Histopathology and histochemistry support the hypothesis that the disease is primarily an infiltrative process.

Early and prolonged corticosteroid therapy may be of benefit.

Our thanks are due to Drs. F. H. Kemp and P. W. E. Sheldon for radiological reports, and to Dr. J. R. P. O'Brien for the biochemical investigations. We are grateful to Mr. E. L. Tugwell for the clinical photographs.

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A STUDY OF 65 CASES OF COMPOUND PRESENTATION

BY

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Although a few isolated cases of compound presentation have been reported in recent years (Claye, 1929; Wong, 1932; Henderson, 1952; King and Mitchell, 1953; Bowles, 1954; Anderson, 1955; Alderman, 1958), only two studies of relatively large series of cases have been presented in the English language—namely, one by Goplerud and Eastman (1953) and the other by Quinlivan (1957). The former made a survey on 65 cases and the latter on 33. A study was therefore made of the 65 cases which occurred in the Tsan Yuk Hospital, Hong Kong, over a period of 14 years (1946 to 1959). Compound presentation is said to occur when one or more extremities, an arm, a leg, or both, prolapse alongside a head which presents, or when one or both upper limbs prolapse alongside a presenting breech.

Incidence

The incidence as shown in the German literature in the nineteenth century varied between 1:1,956 and 1:64 (Pernice, 1858). McCormick (1947) gave an incidence of 1:250, Gibberd (1951) one of 1:800, Goplerud and Eastman (1953) one of 1:652, and Quinlivan (1957) one of 1:360 in St. James' Hospital, London, and one of 1:500 in Hillingdon Hospital, Uxbridge, Middlesex.

In the years 1946 to 1959 inclusive there were 85,879 deliveries in the Tsan Yuk Hospital. In this same period 65 cases of compound presentation were encountered,

thus giving an incidence of 1:1,321, a much lower incidence than those previously reported. Some cases may have spontaneously corrected themselves and therefore been overlooked. The several varieties of compound presentation encountered in this series are compared with Goplerud's series in Table I.

TABLE I.—*Varieties of Compound Presentation*

	No. of Cases in Present Series	No. of Cases in Goplerud's Series
Vertex	57 (8)	55 (13)
Vertex and hand (arm) ..	51 (8)	49 (11)
,, hand (arm), and leg ..	3	4 (1)
,, and foot	3	2 (1)
Breech and hand	7 (2)	4 (1)
Face ,, ,, ...	1	6 (1)
	65	65

In Tables I–III the figures in parentheses denote cases that were associated with prolapse of cord.

Aetiology

Multiparity, size of foetus, multiple pregnancy, placenta praevia, contracted pelvis, and hydramnios were found to be important predisposing factors. All of them are in fact conditions which may prevent complete filling and occlusion of the pelvic inlet by the presenting part. Intervention such as version, either external or internal, performed for any of a variety of reasons, may, if not completed successfully, end in a compound presentation. None of the cases in this series had had a version performed before the diagnosis of compound presentation was made.

Fifty-four (83%) of the patients were multiparae, among whom 11 had had five or more previous premature or full-time deliveries.

Twenty-seven (41.5%) of the babies were premature (1,000 to 2,350 g.). This rate was five times the prematurity rate (8.4%) in Tsan Yuk Hospital over the same period

In this series 18 (27.7%) cases were associated with twin pregnancy; the hospital incidence was 1% (or 1:98.5). The second twin was, as expected, more commonly involved (16 out of the 18 cases). Three (4.6%) cases were associated with placenta praevia; the hospital incidence was 0.6% (528 cases in 85,879 deliveries). Contracted pelvis was found in 4 (6.1%) of the 65 cases; the hospital incidence was 2.1% (1,852 cases in 85,879 deliveries). Hydramnios was present in two cases (3%); the hospital incidence was 0.2% (175 cases in 85,879 deliveries).

Diagnosis

Compound presentation may be suspected when the foetal head remains high and sometimes deviated slightly from the midline or when there is early rupture of membranes, but a definite diagnosis can only be made by either a vaginal examination or a plain *x*-ray film of the abdomen. If a compound presentation is suspected vaginal examination should be performed as soon as possible after rupture of the membranes to confirm or refute the diagnosis and also to ascertain any prolapse of the umbilical cord. The diagnosis of compound presentation was made at full dilatation in 41 (63%) of the 65 cases. None was made before the onset of labour.

Complications

Prolapse of cord is commonly encountered in cases with compound presentation. This is not surprising, for the predisposing causes of the one are exactly the same as those of the other—namely, those conditions which prevent engagement of the presenting part. The hospital incidence of prolapse of cord during the 14 years was 1 in 282.5 cases (0.36%). Ten cases of prolapse of cord were encountered in this series of 65 cases of compound presentation, giving an incidence of 1:6.5 cases (15.4%). Prolapse of cord was therefore encountered more than 40 times as often in compound presentation as would be ordinarily expected.

Uterine inertia has been said to be a common complication of compound presentation. This has not been borne out in the present series of cases. The longest first stage lasted 38½ hours. The first stage lasted more than 24 hours in only three cases, 12 to 24 hours in 11, and less than 12 hours in 46.

Post-partum haemorrhage was present in 3 (4.6%) of the 65 cases, in contrast to the hospital incidence of 1.2%. Two of these occurred in twin pregnancies. Retained placenta which necessitated manual removal was present also in three cases, giving an incidence of 4.6%, in contrast to the hospital incidence of 0.8%. The association of post-partum haemorrhage and retained placenta with compound presentation may be just incidental.

Prognosis

The hazards to the mother are said to be substantially augmented by the danger of a rupture of the uterus. Reviewing the three cases of uterine rupture in their series of 65 cases of compound presentation, Goplerud and Eastman (1953) came to the conclusion that the uterine ruptures were the result of reprehensible obstetric management rather than of the compound presentation itself. Not a single case of uterine rupture occurred in the present series. Only three cases of maternal morbidity were encountered: one was a case of typhoid, one a case of breast engorgement, and one a case of possible genital infection.

Foetal prognosis is known to be bad and foetal mortality high. These facts are confirmed by a study of the present series. The neonatal death rate and the stillbirth rate were 16.7% and 16.9% respectively, in contrast to the respective hospital rates of 1.6% and 2%. But if cases of prematurity and prolapse of cord and one case of anencephaly are excluded, the perinatal mortality that can be attributed to compound presentation *per se* is low: 1 stillbirth in 33 cases (3.3%, or 33 per 1,000), which agrees exactly with the figure given by Goplerud and Eastman (1953). Prolapse of cord, prematurity, prolapse of foot with or without prolapse of hand, twin pregnancy, and the type of management are found to affect the foetal prognosis.

The foetal mortality was 40% in cases with prolapse of cord in contrast to one of 24.6% in cases without prolapse of cord. Prolapse of cord was relatively more common in premature than in mature deliveries.

Prematurity *per se* was responsible for a large proportion of foetal deaths. Sixteen of the 20 foetal deaths (neonatal deaths and stillbirths) occurred in premature babies. Of the 27 premature babies, 11 survived, 8 died neonatally, and 8 were stillbirths, giving a foetal loss of 69.3%.

There is general agreement that foetal mortality is greater when a foot prolapses than when a hand presents. As shown in Table I, of the 57 cases of vertex presentation, 51 were associated with prolapse of hand and 6

with prolapse of foot. The foetal mortality was 25.5% when the hand alone prolapsed, but 66% when the foot prolapsed.

There were two neonatal deaths and two stillbirths among the 18 twin deliveries, giving a foetal loss of 22.2%. Of the four deaths, three occurred in premature babies. Twin pregnancy *per se* does not appear to worsen the prognosis. As a matter of fact, a premature twin stands a better chance of survival than a single premature foetus (30% in contrast to an overall foetal loss of 69.3% in the premature group).

In 23 of the 65 cases no intervention was necessary, and deliveries were spontaneous. Of the 65 cases, 20 were treated only by replacement of the prolapsed limb; all of these 20 patients then delivered spontaneously. Altogether 26 attempts at replacement of the prolapsed limb were made. Three of them were followed immediately by forceps delivery and the other three were unsuccessful. Of the three unsuccessful attempts one was followed an hour later by a successful attempt, and the other two subsequently had spontaneous deliveries. Seven cases were delivered by internal version and breech extraction. Six of the seven cases of breech presentation were delivered by breech extraction (the other one was associated with placenta praevia and was delivered by caesarean section). In all, five women were delivered by caesarean section (including the one just mentioned) and four by forceps (three of them preceded by replacement of the prolapsed limb). The indications for caesarean section were: placenta praevia in one case, contracted pelvis in two cases, prolapse of cord in one, and contracted pelvis together with prolapse of cord in one. The foetal loss in relation to various types of management is shown in Table II.

In order to find out the effect of the type of management on the foetal prognosis, the foetal mortality is analysed in Table III, excluding cases of prematurity, and in Table IV, excluding cases with prolapse of cord and with placenta praevia, and one case of anencephaly.

TABLE II.—*Foetal Loss in Various Types of Management*

	No Treatment	Replacement of Prolapsed Part	Version and Extraction	Breech Extraction	Caesarean Section	Forceps
No. of cases	23	20	7	6	5	4
Living	16 (1)	16 (1)	1	5 (1)	4 (2)	3 (1)
Neonatal death	2	3	2	1 (1)	1	0
Stillbirth	5 (1)	1	4 (2)	0	0	1
Total foetal loss	30%	20%	86%	16%	20%	25%

TABLE III.—*Foetal Loss in Various Types of Management (Excluding Premature Cases)*

	No Treatment	Replacement of Prolapsed Part	Version and Extraction	Breech Extraction	Caesarean Section	Forceps
No. of cases	14	11	4	3	4	2
Living	13	11 (1)	1	3	4 (2)	2
Neonatal death	0	0	1	0	0	0
Stillbirth	1 (1)	0	2 (1)	0	0	0
Total foetal loss	7%	0	75%	0	0	0

TABLE IV.—*Foetal Loss in Various Types of Management (Excluding Cases with Prolapse of Cord, Placenta Praevia, and Congenital Abnormality)*

	No Treatment	Replacement of Prolapsed Part	Version and Extraction	Breech Extraction	Caesarean Section	Forceps
No. of cases	21	18	4	4	2	2
Living	15	15	1	4	2	2
Neonatal death	2	2	1	0	0	0
Stillbirth	4	1	2	0	0	0
Total foetal loss	29%	17%	75%	0	0	0

After consideration of all the available data, the following suggestions are made: (*a*) The best method of managing cases of compound presentation without complications, such as prolapse of cord and placenta praevia, is careful observation with no manipulation. (*b*) Replacement of hand gives equally good results. (*c*) Version and extraction has a very limited place in the management of compound presentation. It is the most dangerous form of management from the viewpoint of both mother and child. (*d*) Breech extraction is advisable for cases where the breech presents, the cervix is fully dilated, and complications such as pelvic contraction are excluded. (*e*) Caesarean section is indicated in cases of placenta praevia, in contracted pelvis, and also when prolapse of cord is detected before full dilatation of cervix (*f*) In cases of compound presentation with prolapse of cord, the management is that of prolapsed cord—namely, caesarean section before full dilatation of the cervix and forceps or breech extraction after full dilatation. (*g*) The correct management of twin pregnancy and delivery and that of premature babies will further reduce the foetal loss.

Summary

Sixty-five cases of compound presentation that occurred in the Tsan Yuk Hospital over a period of 14 years (1946 to 1959) have been studied.

As there were 85,879 deliveries over this same period, the incidence of compound presentation was 1 in 1,321 deliveries.

Multiparity, small size of the foetus, multiple pregnancy, placenta praevia, contracted pelvis, and hydramnios were found to be important predisposing factors.

The diagnosis of compound presentation was made at full dilatation in almost two-thirds of the cases.

Prolapse of cord is commonly encountered in cases with compound presentation.

Compound presentation *per se* does not seem to affect the mother adversely. Foetal prognosis, too, does not seem to be affected by compound presentation, but it is adversely affected by prolapse of cord, prematurity, prolapse of foot, and the type of management given.

Some suggestions regarding treatment are made after consideration of all the available data.

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SKIN PIGMENTATION AND THE MENSTRUAL CYCLE

BY

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Dermatologists have been aware of a facial pigmentation which develops in apparently normal girls at puberty, and which waxes and wanes with each menstrual period, since Brocq (1923) first described such a condition under the name of "erythrose péribuccale pigmentaire." Comments on this disorder are few outside the French literature (Ingram and Brain, 1957), although it is probably not an uncommon condition (*British Medical Journal*, 1952). Its characteristic features (Ingram and Brain, 1957) are the localization to the central part of the face of a relatively constant reddish or yellowish-brown pigmentation. A perioral ring of pale skin is sometimes seen, and it may be possible to blanch some of this coloration by diascopic pressure. This last feature suggests an element of vasomotor instability in the condition. There may, however, be a more diffuse mottling of discoloration noticeable, especially across the forehead (MacKenna, 1952).

Goldsmith and Hellier (1954), citing Edwards and Duntley (1949), mentioned that the skin of women is more sensitive to ultra-violet light and is more vascular during the premenstrual phase of the menstrual cycle. They also describe the occurrence of a chloasma in non-pregnant females and draw attention to a heredofamilial factor in the predisposition of patients to this condition. The condition was said to be an essentially normal phenomenon by Poor (1930), who described a macular seborrhoea in association with the brownish or blackish pigmentation. Poor noted that the pigmentation occurred in young girls at the time of the first menstrual period and that it was situated chiefly round the mouth but involved other parts of the face.

Ormsby and Montgomery (1954) made a distinction between Brocq's pigmentation and that variety described by Poor. They believed that Brocq's pigmentation may be pathological whereas Poor's pigmentation is a purely physiological phenomenon. They encountered facial pigmentation in patients with ovarian neoplasms, functional diseases of the uterus, and in cases of "disease of endocrine imbalance." Daily and even hourly fluctuation in the intensity of the pigmentation was described by these writers in their cases, and they attributed the changes to endocrine and nervous imbalance.

The physiological facial pigmentation described by Poor occurred in normal young females and was not a sign of disease. Poor called the condition "chloasma periorale virginium." His associate, Von Verde (1930), added a further series of similar cases which were characterized by pigmented macules about the mouth occasionally spreading to other parts of the face and appearing in young virgins. Von Verde believed that the pigmentation was related to ovarian function and found that, although the cases were resistant to all forms of treatment, he believed the condition usually disappeared spontaneously after some years.

A further series of cases was described shortly after this by Ormsby and Ebert (1930, 1931), who drew attention to the darkening of facial pigmentation immediately before the menstrual period began. Occasional case reports and comments on the condition have appeared in journals since then.

All writers mention the probable importance of the endocrine glands in the genesis of fluctuating facial pigmentation, and Brocq himself suspected this. However, hitherto no one appears to have related the pituitary melanocyte-stimulating hormone (M.S.H.) to this condition. This is readily understandable in view of the relatively recent advent of experimental work on the properties of M.S.H. and its secretion in health and disease. Final elucidation of the relationship between M.S.H. and changes in normal pigmentation can only be expected when methods of extraction, purification, and measurement of the hormone are reliable beyond doubt and easy to perform.

In a previously documented study I was unable to demonstrate consistent changes in the serum M.S.H. levels of normal women in relation to their menstrual cycles (McGuinness, 1959). This was probably because of difficulty with the methods of assay employed. It is believed that regular changes in pituitary M.S.H. production are likely to occur normally despite the present lack of convincing laboratory evidence in support of this.

Apologia for the Present Study

If these fluctuations in the secretion of M.S.H. do in fact occur and are effective in producing a regular pattern of changes in skin pigmentation, a critical survey of the day-to-day appearances of a number of normal persons might be expected to reveal evidence of this.

There are no references in the literature to such a survey ever having been conducted. Therefore, a small survey of female medical students and medical practitioners aged 19 to 30 years was carried out by questionary. The object of this was to find out whether pigmentary variations could be detected in normal females and whether changes in the intensity of the pigmentation were related to the phases of the menstrual cycle. The subjects, as a special group in the community, were chosen because their trained skill in observation and knowledge of the physiological background to the study made it likely that the results they recorded would be accurate and therefore of value in assessing the problem under investigation.

Methods.—The survey was begun in March, observations being made by the subjects from then onwards through the spring and summer months, the data being collected for analysis in October. Comments based on the results of this survey therefore depend on observations made over the course of about six months. Out of 120 subjects circularized, 63 replied. Each subject received a simple form which outlined the purpose of the inquiry, specified the observations required in the form of simple unambiguous questions, and explained by simple notes how the observations were to be recorded. The specimen form on the next page shows the exact arrangement and wording of the questionary.

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Specimen Form

SURVEY ON SKIN PIGMENTATION IN RELATION TO THE MENSTRUAL CYCLE

DEPARTMENT OF PATHOLOGY. LIVERPOOL UNIVERSITY.

Introduction

Relatively recently there has been described a pigmentation of the face developing in females at puberty and attributable to pituitary M.S.H. production.

To a critical observer skin pigmentation might be seen to vary with the menstrual cycle as pituitary function fluctuates.

No data have ever been assembled to investigate this possibility, and this inquiry is an attempt to assess the matter in normal women.

This is at present part of the work being undertaken in this department on pigment-producing hormones.

You are requested to fill in this form after observing your skin colour during the next six months.

Negative answers are just as important as positive ones.

The form should be returned to this department in the envelope provided.

Your name is not required, identification of subjects being by numbers only.

Questions

A
1. Age
2. Hair colour
3. Previous illnesses
4. Present health

B
1. Do you tan readily in the sun ?
2. How many hours' exposure to sun gives you minimal tanning ?
3. How long does pigmentation persist after your last exposure to strong sunlight ?
   (*a*) Minimal tanning
   (*b*) Marked tanning

Has your skin colour in the following regions changed in relation to the menstrual cycle ?

C
1. Forehead
2. Round the mouth
3. Round the eyes
4. Axilla
5. Areola of nipple
6. Abdomen, especially linea alba

D
1. Age of menarche
2. Is the menstrual cycle regular ?
3. Do you have any symptoms referable to changing hormone levels—e.g., premenstrual tension syndrome

Notes

In part A mention especially skin and endocrine conditions.

The questions in part B are to assess target-organ sensitivity. Minimal tanning is just sufficient to distinguish between adjacent exposed and non-exposed areas (e.g., above and below the collar). Marked tanning is sufficient to be obvious to the subject when exposed skin is examined without reference to unexposed skin.

Specimen answer to part C: "Forehead becomes noticeably darker 2 days before the M.P. is due, and this persists for about 10 days."

Results

Tables I–V summarize the results obtained. The findings are classified in relation to the occurrence or otherwise of varying skin pigmentations. It will be seen that about half the women questioned had some increase in skin pigmentation, which was noted in every case in the latter days of the menstrual cycle and in some cases during menstruation also. The others showed no skin changes whatsoever.

There was no correlation between hair colour and varying skin pigmentation, nor between this and the age of the menarche. The presence or absence of premenstrual symptoms was not related to skin shade. The sensitivity of the subjects' skin to ultra-violet light, as assessed by the speed of darkening in sunlight and the duration that tanning persisted, did appear to have a

TABLE I.—*Relationship of Hair Colour and Ultra-violet-light Skin Sensitivity to the Skin-pigment Changes of the Menstrual Cycle*

Indices of the Factor Under Consideration	Fluctuation in Skin Pigmentation in Relation to Menstrual Cycle		
	Changes Observed	No Changes Observed	Total
Total in series	29	34	63
Hair colour:			
Black (brunette)	2	5	7
Brown (light and dark)	24	25	49
Fair (blonde)	2	1	3
Red (auburn)	1	3	4
Skin sensitivity to ultra-violet radiation:			
(*a*) Speed of response measured by time of exposure required to produce minimum tanning:			
Rapid: <2 hours	5	3	8
Moderate: 2–12 hours	21	16	37
Slow: >12 hours	2	12	14
No response: Infinite	1	3	4
(*b*) Persistence of tanning after last exposure to direct strong sunlight:			
Minimum tanning:			
<1 week	6	11	17
1–3 weeks	6	12	18
1–3 months	17	11	28
4–6 ,,	0	0	0
>6 ,,	0	0	0
Marked tanning:			
<1 week	8	14	22
1–3 weeks	9	14	23
1–3 months	6	6	12
4–6 ,,	3	0	3
>6 ,,	3	0	3

Minimum tanning is pigmentation just sufficient to distinguish between adjacent exposed and non-exposed areas—for example, above and below the collar. Marked tanning is pigmentation sufficiently dark to be obvious to the subject when exposed skin is examined without reference to unexposed skin.

TABLE II.—*Relative Frequency of Pigmentation at Several Sites*

Site	No. Affected
Forehead	8
Perioral	10
Periocular	25
Axilla	5
Areola of nipple	17
Abdomen: linea alba	6
No. with multiple site changes	19

TABLE III.—*Frequency of Sites Involved in Combination*

Site Combinations	No.
Periocular and nipple	11
,, ,, forehead and perioral	6
Axilla and nipple	2
,, ,, ,, and abdomen	2
Other combinations	0

The sites most commonly affected by this pigmentation are the periocular skin and nipple areola. Other sites are affected in 35% or less of subjects. Involvement in more than one place is common.

TABLE IV.—*Age of Menarche in Relation to Variation of Skin Pigmentation with Menstrual Cycle*

Age of Menarche to Nearest Year Above	Pigment Changes Observed	No Pigment Changes Observed	Total
12 and under	1	1	2
13–15	19	26	45
16–18	8	7	15
19–21	1	0	1
Over 21	0	0	0

TABLE V.—*Premenstrual Symptoms, Referable to Changing Hormone Levels, in Relation to Facial Pigmentation that Varies with Menstrual Cycle*

Symptoms Referable to Changing Hormone Levels	Pigment Changes Observed	No Pigment Changes Observed	Total Cases
Primarily organic:			
Full premenstrual tension syndrome	5	4	9
Gastro-intestinal disturbance alone	0	1	1
Frequency of micturition alone	0	0	0
Exacerbation of acne	3	6	9
Primarily psychological:			
Irritability	0	0	0
Depression	5	7	12
Malaise	6	3	9
Headache	2	2	4
No symptoms	8	11	19

bearing on the problem. Thus those subjects showing changes in skin pigmentation related to the menstrual cycle tended to have skin that pigmented more readily and more persistently than those in the other group. But there were exceptions to this general tendency in both groups; a few "pigmenting" subjects tanned slowly in the sunlight and lost their tan relatively quickly; a few "non-pigmenting" subjects tanned quickly and retained their tan a long time.

The site most commonly showing pigmentation changes was the skin around the eyes. Next most frequently affected were the areola of the nipple and the perioral skin. The forehead, axilla, and abdomen were affected in less than one-third of the "positive" subjects. Nineteen out of 29 subjects showed changes in more than one place. The commonest combination of sites was that of periocular skin with nipple areola skin.

Discussion

This survey was carried out on a group of young female subjects selected for training in scientific observation and for their understanding of the background to the work. It demonstrated that pigmentation of the skin varied in relation to the menstrual cycle in about half the women assessed. The periocular and nipple areola skin was most commonly affected, skin darkening occurring during the week preceding menstruation, and in some cases during menstruation also. Skin sensitivity to ultra-violet light was of importance in determining the occurrence of this phenomenon, but none of the other factors examined had any influence upon it. Although this is a small series, the conclusions based upon it probably apply to women in the general population, thus indicating that skin pigmentation varying in intensity, in time with the menstrual cycle, may well be a common normal condition.

There is a certain amount of evidence from experimental work (Collin and Drouet, 1933; Cunningham Dax, 1938; Lambillon and Lejeune, 1938; Shizume and Lerner, 1954) that this phenomenon may be referable to variations in the secretion of M.S.H. by the pituitary. Since the pituitary produces several hormones in a cyclical fashion, thus, for example, governing the cyclical pattern of the menses, it is not unreasonable to postulate that cyclical variation in M.S.H. secretion, in keeping with general pituitary behaviour, may also occur. Thus this apparently common cyclical variation of skin pigmentation found in young women may well have its origin in the fundamental cyclical activity of the master endocrine gland.

Summary

A pigmentation of the skin varying in intensity in a constant relationship with the phases of the menstrual cycle has been recognized by clinicians for many years. The pattern of this variation and its occurrence in normal young women has been demonstrated by a simple survey technique. The occurrence of the skin condition appears to be related to the sensitivity of the skin to ultra-violet light, darkening of the skin always occurring in the premenstrual week. Although the explanation of this phenomenon is not clear it seems likely that changes in the secretion of the melanocyte-stimulating hormone by the pituitary are responsible for this interesting and probably common condition.

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Preliminary Communications

Treatment of Petit Mal with Ethosuximide

Recent years have seen the search for an effective drug to control petit mal. The oxazolidine-dione compounds (troxidone and its allies) have given encouraging results in many cases but they have the disadvantage of being apt to produce unpleasant side-effects and occasionally severe damage to the bone-marrow with consequent agranulocytosis. Derivatives of the basic succinimide molecule have subsequently been investigated. The first was phensuximide ("milontin"), but, although apparently without any serious side-effects, its therapeutic effect in petit mal has on the whole been disappointing. The same applies to its successor, methsuximide ("celontin"). The most recently synthesized drug in this series is α-ethyl-α-methylsuccinimide, which has the approved name of ethosuximide. It is marketed in this country as "zarontin" and "emeside" in soluble gelatin capsules, each containing 250 mg. of ethosuximide.

Preliminary investigations in the U.S.A. showed that ethosuximide was without toxic effect when given by mouth to animals for 12 months. Zimmerman and Burgemeister (1958) produced the first clinical report of the use of ethosuximide in epilepsy. They regarded it as "essentially a petit mal drug" and were able to control the attacks completely or almost completely in two-thirds of their cases. Vossen (1958) next reported good results in some 39% of the 56 patients with petit mal, his observation period ranging from 3 to 18 months. Lorentz de Haas and Stoel (1960) obtained good results in about 47% of 60 patients. Gordon (1961) reported favourably on the value of ethosuximide in the treatment of pure petit mal (in the absence of brain damage) in a small group of cases.

No serious toxic effects have been reported by any of these workers, though occasional nausea or vomiting

on starting treatment has been noted. Of Zimmerman and Burgemeister's 109 patients, 9% experienced side-effects that were usually related to high dosage and were relieved by reduction of the dose. These symptoms included nausea, gastric discomfort, drowsiness, and dizziness. Skin rashes have not been observed and no significant haematological or urinary changes have been recorded in any patients treated.

PRESENT SERIES

No accounts of the use of ethosuximide have so far been published in this country, and the present communication deals with 50 hospital out-patients who have been treated with this drug. All of them suffered from petit mal and 19 had also had grand mal convulsions at some time. The petit mal was generally of the classical form, consisting simply of transient loss of awareness without falling, but it was sometimes associated with momentary jerking of the head or arms, or with a brief akinetic attack in which the subject fell limply to the ground and then quickly got up again. Routine electroencephalograms were not made, but classical 3-per-second wave-and-spike records were obtained in 22 cases. Sixteen patients gave a family history of epilepsy; 36 were under 20 years of age; and 40 had been subject to petit mal for more than one year before treatment with ethosuximide was begun. None had responded satisfactorily to other drugs. Almost all had already been treated with phenobarbitone and 27 of them had also had troxidone, aloxidone, phensuximide, or amphetamine. A few had had all these.

Ethosuximide was prescribed in addition to whatever antiepileptic drugs the patient was already taking, and the initial dose was generally one capsule (250 mg.) two or three times daily. Sometimes the dosage was gradually increased up to six capsules daily, but those who responded satisfactorily to the drug usually did so quickly with smaller doses of three or four capsules daily. When a satisfactory response was obtained, other drugs were gradually stopped, if feasible, and eventually in a few cases where control of attacks seemed complete the ethosuximide itself was gradually stopped. Results of treatment in our 50 cases were: 27 successfully controlled, 10 partially and inadequately controlled, and 13 unaffected.

Of the 27 cases described as "successfully controlled," 21 have remained completely free from attacks for an average period of 10 months. The distribution of these periods was: 3 to 12 months in 12 cases, 12 to 18 months in 4, and 18 to 24 months in 5. The other six patients have been almost completely free from petit mal attacks for an average of eight and a half months. They have had only occasional attacks (about once a month, usually after some special provocation such as omission of capsules, undue fatigue, or excitement) whereas previously they had usually had several daily.

Of the 27 successfully treated patients, 15 had been subject to petit mal for three years or longer before starting ethosuximide. The drug was not noted to have any provocative or therapeutic effect on grand mal in this series.

The effective daily dosage of ethosuximide in the successfully treated cases was: one capsule in 2 cases, two capsules in 2 cases, three in 15 cases, four in 4 cases, five in 1 case, and six in 3 cases.

In seven instances it has been possible to withdraw the ethosuximide gradually after about six months, without recurrence of petit mal. These patients have now been without any treatment for an average of 12 months, although previously they were having frequent attacks. In other cases, however, reducing or stopping ethosuximide has led to temporary recurrence of petit mal until the drug has been restored.

The following is an illustrative case history:

A boy born in 1946 and first seen in 1955 had had typical petit mal up to four or five times daily for one year and was treated unsuccessfully with phenobarbitone, amphetamine, and troxidone in turn. Troxidone had to be stopped because of leucopenia, and he was then given phensuximide. There was some temporary improvement, but after six months' treatment with phensuximide he was having six or more attacks daily. In July, 1959, when he started taking ethosuximide (three capsules daily), he was having about 16 petit mal attacks a day. These continued for the first three days of treatment, but since then he has remained completely free of them. As he felt sick and sleepy at the beginning of this treatment, the dose was reduced to two capsules daily. He became alert and remained well. In March, 1960, the drug was stopped and there has been no recurrence of this petit mal. Serial white counts showed a steady rise in the polymorph count to a normal level after beginning treatment with ethosuximide.

SIDE-EFFECTS

Although we have encountered no serious toxic reactions to ethosuximide, 17 of our patients showed some side-effects when they began to take the drug (14 of these received three capsules daily and three received two capsules daily). Apathy, depression, or drowsiness occurred in eight, nausea in five, vomiting in four, and dizziness and transient stammer each in one case. In five further cases apathy, nausea, or vomiting occurred later, when the dose was increased to four, five, or six capsules daily. These symptoms usually subsided rapidly when the dose of ethosuximide was reduced; treatment then continued normally. In four instances it was thought advisable to stop the drug permanently.

No urinary abnormalities or skin rashes were seen. Blood counts were done in some two-thirds of the patients at some time during treatment and considerable variation from time to time was noted. Occasional polymorph counts of between 2,000 and 3,000/c.mm. were observed, but these were unaccompanied by any clinical manifestations and were not regarded as an indication for reducing the dose. In two cases, although previous oxazolidine-dione therapy had resulted in polymorphonuclear leucopenia, the polymorph counts increased steadily after starting treatment with ethosuximide.

SUMMARY

Fifty patients with petit mal have been treated with ethosuximide and in 27 of these the attacks have been successfully controlled for periods of up to two years.

The effective dosage in the majority of patients was one capsule (250 mg.) three times daily.

No serious toxic reactions have been seen but transient side-effects may occur, especially at the start of treatment. The initial dosage should therefore not exceed one capsule daily for small children and two capsules daily for older children and adults.

We are grateful to Messrs. Parke, Davis and Co., who kindly supplied capsules of ethosuximide (zarontin) for this trial.

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Medical Memoranda

Aorto-duodenal Fistula after Surgery of Abdominal Aorta

The following case histories are presented to draw attention to the occurrence of aorto-enteric fistula as a sequel to reconstructive operations such as thrombo-endarterectomy or grafting of the abdominal aorta, for when such a complication occurs the patient may present with symptoms and signs of gastro-intestinal haemorrhage. The complication has occurred in approximately 2% of our cases.

CASE REPORTS

Case 1.—In April, 1958, a 58-year-old man presented with an aneurysm of the abdominal aorta which was treated by resection and insertion of a nylon prosthesis. His convalescence was complicated by the development of a small-bowel obstruction due to adhesions, wound sepsis, a pelvic abscess, and a deep-vein thrombosis in the left leg. He was discharged from hospital seven weeks after operation. In August he was admitted to another hospital and an operation was performed for a small-bowel obstruction due to adhesions. The post-operative course was apparently complicated by a staphylococcal septicaemia. In May, 1959, he developed sudden abdominal pain, collapsed, and died. Necropsy showed that the proximal graft anastomosis had ruptured into the posterior aspect of the third part of the duodenum, and the stomach and small gut were filled with blood. There was also extensive clot in the retroperitoneal tissues and right psoas sheath.

Case 2.—A 57-year-old man developed intermittent claudication in the thighs and calves which stopped him walking after 50 yards. The common femoral pulses were reduced and no other pulses were palpable in the lower limbs; aortography confirmed the presence of an atherosclerotic occlusion of the aorta and common iliac arteries. In December, 1958, thrombo-endarterectomy of the lower aorta and common iliac arteries was carried out with complete relief of the claudication and restoration of popliteal and ankle pulses; the patient returned home on the 19th day after operation. A month later he started to complain of intermittent epigastric and para-umbilical pain; physical examination was negative and a barium-meal examination revealed nothing abnormal. In April, 1959, he had a haematemesis and was treated medically in hospital for six weeks. In July he was admitted to another hospital with a recurrence of the haematemesis; an emergency partial gastrectomy was carried out, but he died. Necropsy showed that the cause of the gastro-intestinal haemorrhage was a fistula between the right common iliac artery at the line of suture and the third part of the duodenum.

COMMENT

Reported cases of aorto-enteric fistula occurring after reconstruction operations on the abdominal aorta are few and relate mainly to the use of homografts. In an analysis of 120 consecutive cases of major arterial grafts Humphries *et al.* (1956) noted two instances in which freeze-dried homografts had ruptured into the duodenum and one case of rupture into the jejunum. DeWeese *et al.* (1959) also recorded two cases of aortic homograft failure with rupture into the jejunum. In the case described by Hagland *et al.* (1959) the patient was found to have a duodenal ulcer and was submitted to partial gastrectomy before it was realized that the cause of his gastro-intestinal haemorrhage was rupture of an aortic homograft into the ileum.

While the reports from the literature suggest graft failure as the cause of fistula formation, it seems probable that the friable nature and poor suturing qualities of the atherosclerotic aorta are of even greater importance, and it is perhaps surprising that the complication does not occur with greater frequency. The third part of the duodenum is at a much lower level than is generally realized and must often be reflected upwards to expose the aortic bifurcation. Where fistula formation takes place this part of the duodenum, which is unprotected by peritoneum, would appear to be especially vulnerable, irrespective of whether a grafting procedure or thrombo-endarterectomy has been carried out.

Aorto-enteric fistula should be regarded as a likely cause of gastro-intestinal bleeding in patients who have been submitted to reconstructive surgery of the abdominal aorta, for as survival rates for such operations improve it may be that this complication will be seen more often.

We are indebted to Dr. H. F. Barnard and Dr. J. Adler for the post-mortem reports.

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Humphries, A. W., De Wolfe, V. G., and LeFevre, F. A. (1956). *J. Amer. med. Ass.*, **161**, 953.

A revised British Standard—Methods for Determination of Air Pollution (B.S.1747: 1961), Part 1. Specifications for Deposit Gauges—has now been published. When it was first published in 1951 it was concerned solely with deposit gauges. Now it is being reissued in several parts to cover, in addition, apparatus and procedure for the measurement of (1) fine particles (smoke), and (2) gaseous impurities, as well as the solid material (such as grit) which is measured by the deposit gauges specified in Part 1 of the standard. Experience in the use of deposit gauges during the past ten years has enabled the British Standards Institution committee concerned to introduce a number of refinements into the standard, but the procedure outlined is substantially unchanged. The standard deals with the construction, installation, and use of deposit gauges. A standard report form and a statement of the analytical determinations to be made are included. Copies may be obtained from the British Standards Institution, Sales Branch, 2 Park Street, London W.1, price 5s. each, postage extra to non-subscribers.

Reviews

DESIGN OF RESEARCH LABS.

The Design of Research Laboratories. The Report of a Study carried out by the Division for Architectural Studies of the Nuffield Foundation. (Pp. 211+xx; illustrated. 45s.) London, New York, Toronto: Oxford University Press. 1961.

This report on the function and design of research laboratories is not specially concerned with medical laboratories. Indeed, the surveys were carried out in the laboratories of the Agricultural Research Council, Imperial Chemical Industries, Glaxo Laboratories, and the Distillers Company. Nevertheless, it will be of value to all those who are concerned with the design of laboratories in the forthcoming expansion of our hospitals and universities.

It is well produced, on a large page, and there is a delightful historical introduction, showing men in top hats and beards working at laboratory benches in the early nineteenth century, from which one learns that buildings specially designed for research purposes did not appear until the nineteen-twenties. Another well-illustrated chapter gives good examples of current practice in laboratory design. The main body of the book deals with the design of general laboratories and special-purpose rooms, engineering services, lighting and colour, and problems such as noise, vibration, and fire and safety precautions. The book contains a great deal of useful information and should be studied by anyone having responsibility for a new laboratory.

Any criticisms are minor ones. It is probable that a second edition would give more attention to the use of radioactive materials. While there has been a good deal of study of the space required per individual, there has been much less study of the overall size of laboratory rooms. It is shown that the minimum economic unit is two or three workers, and further economies are achieved with four or five workers; but it would have been interesting to have information about the advantages and disadvantages of still larger rooms. The difficult problem of space for writing is touched upon; clearly there must be some writing space in the working laboratory, but it is desirable for the man writing a paper or a thesis to be able to get right way from the laboratory bench. There is little about staff rooms and seminar rooms, which are quite essential.

In medicine, finally, we cannot afford to think of ward units or laboratories in isolation, but must see them in the context of the hospital or the university. In some new hospital building in Germany at the present time the facilities for examining patients and making laboratory studies are just as rigidly separated from the ward blocks as is the nurses' home, and research and teaching in the universities are also deliberately separated. These separations seem open to criticism, and the physical relation of research laboratories in the medical schools to routine laboratories, teaching space, and wards would be an interesting subject for discussion.

L. J. WITTS.

DERMATOLOGY WITHOUT TEARS

A Manual of Cutaneous Medicine. By Donald M. Pillsbury, M.A., D.Sc.(Hon.), M.D., F.A.C.S., Walter B. Shelley, M.D., Ph.D., F.A.C.P., Albert M. Kligman, M.D., Ph.D. (Pp. 430+xii; illustrated. 63s. 6d.) Philadelphia, London: W. B. Saunders Company. 1961.

Five years ago the authors of this work published a textbook which gave dermatology a "new look" and made it intelligible to the general medical reader. It rapidly took its place as a major contribution in medicine. The present reasonably priced handbook is equally significant, and will be of value to students, undergraduate and postgraduate, in all fields of medicine, clinical and pre-clinical. It is not a mere précis of the larger work, but it approaches the subject in the same way as part of general medicine and incorporates the great advances which have been made in our knowledge of basic anatomy and physiology and in our understanding of clinical problems and their treatment.

The first 50 pages present a lucid and fascinating account of the skin as a dynamic organ, which explains not only the subsequent clinical behaviour of the organ but much that is important in physiology and general medicine. A further 25 pages on diagnosis are the best that have been written on this subject. The commonsense approach on general lines without the jargon and confusing terminology of a specialty is refreshing.

The major part of this work is naturally devoted to the clinical field, and "cutaneous medicine" is the appropriate title. The considerations, presentation, and management are those of a general physician, and are exemplified by the fact that terms like eczema, psoriasis, and seborrhoeic dermatitis do not appear in the chapter contents listed at the front of the work. This does not mean that they are not dealt with in the text, but that they assume their proper interpretation in relation to medicine as a whole rather than being presented as disease entities. The whole field of significant clinical dermatology is covered in 300 pages. This is most readable: the straightforward, simple, and practical approach is attractive, there are no superfluous frills, and the language is devoid of meaningless terms and clichés. The overall merit of this work is great, and the illustrations in black-and-white are excellent and numerous. The general departure from the traditional presentation of the subject is most welcome and will certainly set the pattern for future textbooks.

The only criticism that might be raised is the absence of major features of histology in the general text. In the past it has been usual to include much that was valueless and meaningless in this respect, but there is also much of value in the general understanding of histopathology in relation to clinical features and in the broad education in general pathology. In a brief chapter of three pages on basic pathological patterns the authors gave promise of dealing with this facet of dermatology in the same broad general medical fashion in which they had approached the clinical field. The promise was not, however, fulfilled. It would be interesting to see this chapter developed in further editions, and it would be of practical importance to include a few words in the particular clinical sections where the histology illuminates the subject or emphasizes a principle.

This is an important work for every student and practitioner. It is dedicated to Sidney Gross, a brilliant colleague of the authors, who died at the age of 32.

JOHN T. INGRAM.

DIABETES

Diabetes. With a Chapter on Hypoglycaemia. By 54 authors. Edited by Robert H. Williams, M.D. (Pp. 793+xvi; illustrated. $20.) New York: Paul B. Hoeber, Inc. 1960.

This somewhat formidable textbook of nearly 800 pages is the work of 54 authors, many of whom are recognized

authorities on particular aspects of carbohydrate metabolism and diabetes. It is not surprising, therefore, that it contains a large amount of valuable information which cannot be found in any other single volume. For this reason, if for no other, Dr. Williams and his co-authors deserve both our praise and our gratitude.

After an outline of the history of diabetes by Charles Best there are 24 chapters devoted to the scientific aspects of carbohydrate metabolism. It would be invidious to draw distinctions in respect of the merits of individual chapters, and to praise those on "Summation of Insulin Effects," by William Stadie, on "Growth Hormone," by F. G. Young and A. Korner, on "Insulin Antagonism in Plasma," by P. J. Randle, and on "Immunologic Reactions to Insulin," by S. A. Berson and R. S. Yalow, is in no way intended to detract from the many other excellent chapters in this section.

In this type of book the purely scientific aspect of the subject, being largely an account of experimental work, is less open to criticism than are the views and opinions based on clinical experience in the field of diagnosis and treatment. The account of treatment by diet by Alexander Marble is full of sound observations, but, with its emphasis on weighed carbohydrate and measured protein and fats, will seem somewhat unrealistic to many clinicians. The chapter on treatment with insulin is remarkable for the omission of any mention of the routine use of morning and evening injections of soluble insulin, intermediate or long-acting insulins being advocated even in severe diabetes. This view is quite contrary to that of many authorities, including R. D. Lawrence, and is not in accord with the experience of the reviewer or many severe diabetics in Great Britain.

The oral hypoglycaemic agents are well described by the editor, and the treatment of diabetic acidosis follows the usual American practice of giving larger doses of insulin at more frequent intervals than many of us would consider necessary, or, without repeated blood-sugar estimations, without danger. The complications receive uneven attention. The account of renal disease by Robert Kark and Derek Gellman is excellent, while that of retinopathy by Bernard Becker seems, by our standards, somewhat gloomy; diabetic cataract is dismissed in ten lines. The last section of the book is entitled "Hypoglycemosis," and, not surprisingly, is notable chiefly for a terminology which makes it hard to read and harder still to appreciate.

It is obviously impossible in the space of a short review to do justice to a book of such authority and scope, which should be studied, if not read in its entirety, by all physicians interested in the subject of carbohydrate metabolism and diabetes.

WILFRID OAKLEY.

THE ELUSIVE STEM CELL

Der Menschliche Lymphknoten. By Bernfried Leiber. (Pp. 474; illustrated. DM. 248.) Munich and Berlin: Urban and Schwarzenberg. 1961.

In its general format this book is a good example of the publisher's art. Paper and typography are excellent. The illustrations, 549 in all, mainly photomicrographs, of which many are in colour, are for the most part admirable.

The book consists of a text which occupies about 170 pages, and an atlas covering nearly 300 pages. A cursory account of lymph-node development is followed by a brief description of the main groups of lymph nodes in the body. The next section contains a somewhat sketchy account of lymph-node structure and function, together with a discussion of certain aspects of the production and function of the lymphocyte.

The most distinctive feature of the book is the "Schematic Lymphogram," a diagram that consists of contiguous or overlapping circles of various sizes and summarizes the author's views on the relation between the various normal and abnormal cells in lymph nodes. There are four levels of stem cells, of which the first is the elusive "indifferent mesenchymal cell." This gives rise to three sub-orders of stem cells, which can, in turn, follow various lines of specialization. The schematic lymphogram is intended for use in recording pathological changes in lymph nodes. Its value depends upon the accuracy of the author's views on the cellular interrelationships which he depicts. It is noteworthy that, despite the profuseness of the illustrations, no illustration is given of the all-important indifferent mesenchymal cell. It is not found in smears, and the author contents himself with a brief verbal description of it.

This is a singular omission which ought to be rectified, particularly in view of the fundamental importance attached to this cell and the controversy which has centred around it. In the absence of convincing illustrations and precise morphological criteria whereby both the cell and related forms can be clearly recognized a vaguely defined stem cell is all too prone to engender an atmosphere of haematological mysticism.

J. M. YOFFEY.

THORACIC INCISIONS AND EXPOSURES

Techniques of Thoracotomy. By B. T. Le Roux, M.B., Ch.B., F.R.C.S.Ed. Foreword by Sir Clement Price-Thomas, K.C.V.O., F.R.C.S., F.R.C.P., M.D., LL.D. (Pp. 94+xi; illustrated. 55s.) Edinburgh and London: E. and S. Livingstone Ltd. 1961.

The author's aim in this small book is to provide a detailed account of the incisions and exposures used in thoracic surgery. He is not concerned with any of the intrathoracic procedures, and, indeed, what he says is confined to the practice of one well-known school. The text is well illustrated, and the book would provide useful help for any surgeon who is not in the habit of opening the chest, but, as has been said, it does not go beyond this. The various standard exposures are described, and there is an instructive section on the drainage of empyema. Production is admirable.

T. HOLMES SELLORS.

SIXTEENTH-CENTURY DIARY

Beloved Son Felix. The Journal of Felix Platter, a Medical Student in Montpellier in the Sixteenth Century. Translated and introduced by Sean Jennett. Foreword by Jack Lindsay. (Pp. 155; illustrated. 25s.) London: Frederick Muller Limited. 1961.

An honest diary gives a vivid picture of contemporary life. This book is such a record written by Felix Platter during his five years' medical study at the University of Montpellier (1552–1557). It has been well translated and makes good reading.

The father of Felix was not well off, but he arranged for his son to live in the family of a pharmacist called Catalan, receiving and boarding in exchange Catalan's son, who wished to study in Basle. Felix was only 15 years old when he travelled from Basle to Montpellier, the journey on horseback taking 20 days. He was made very welcome by Catalan and proved a good

student, attending lectures, learning how to prepare drugs in the pharmacy, and taking every opportunity to increase his knowledge. He was sociable, played the lute and other instruments, and sometimes joined in excursions to the parts around. He spoke Latin well.

His plain narrative delineates the cruel customs of the time. He saw those charged with heresy carrying on their backs the trusses of hay which were to burn them at the stake, he witnessed malefactors broken on the wheel, beheaded by the axe, or hanged on a gibbet, and he describes with obvious excitement how he helped to exhume corpses from the grave for the purpose of dissection. He mentions that even young girls and monks sometimes attended a public dissection. He wrote to his father when opportunity offered, and on one occasion sent him a prescription for strengthening the memory, but unfortunately he does not mention the ingredients. He refers to an infallible remedy for making the hair grow which, however, failed to make his beard appear. He returned home after five years, managing to visit Paris on the way, and found that he was a head taller than when he had left home. He was a qualified doctor who later became a distinguished physician.

ZACHARY COPE.

A "MUST" FOR "SQUARES"

Progress in Clinical Medicine. By Various Authors. Edited by Raymond Daley, M.A., M.D.Cantab., F.R.C.P., and Henry Miller, M.D.Durh., F.R.C.P., D.P.M. Fourth edition. (Pp. 345+x; illustrated. 50s.) London: J. and A. Churchill Ltd. 1961.

The appearance every four years of a new edition of *Progress in Clinical Medicine* is very welcome. As in previous editions the editors have assembled a team of experts—some of whom have been omitted from the list of contributors—who are free to expand on topics which interest them. Such a book meets a very real need, and, though no attempt is made to be comprehensive or uncomfortably up to date, the overall result makes balanced reading. The section on modern immunological concepts should, because of its great potential importance, be much expanded in the next edition, and one might expect to find some references to aldosterone antagonists more recent than 1958. The last chapter on space medicine is most interesting and timely. It is a "must" for any "square" father who hopes to keep up with his teenage son.

R. I. S. BAYLISS.

BOOKS RECEIVED

Review is not precluded by notice here of books recently received.

Frontiers of Mammary Cancer. The Tenth Macewen Memorial Lecture Delivered in the University of Glasgow on 26th June 1958. By Charles Huggins, M.D., M.Sc.(Yale), D.Sc.(Acadia, Washington, Leeds, Torino). (Pp. 29; illustrated. 7s. 6d.) Glasgow: Jackson, Son and Co. 1961.

Preparation for Retirement. Solving New Problems. By Alastair Heron. (Pp. 28. 2s. 6d.) London: The National Council of Social Service. 1961.

Gowland Hopkins. A Memoir on the Discoverer of Vitamins. By Ernest Baldwin, Ph.D. (Pp. 26; illustrated. No price.) London: Van den Berghs Ltd. 1961.

The Physiology of Emotions. Report of the Third Annual Symposium of the Kaiser Foundation Hospitals in Northern California, San Francisco. Edited by Alexander Simon, M.D., Charles C. Herbert, M.D., and Ruth Straus. (Pp. 248+xii; illustrated. 52s.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications Ltd. 1961.

Myasthenia Gravis. The Second International Symposium Proceedings. Edited by Henry R. Viets, M.D. (Pp. 707+xxiii; illustrated. £11 12s.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications Ltd. 1961.

Good Health in the Tropics. Advice to Travellers and Settlers. By W. H. Jopling, M.R.C.P.(Lond.), M.R.C.P.(Edin.), D.T.M.&H.(Eng.). (Pp. 31. 3s. 6d.) Bristol: John Wright and Sons Ltd. 1961.

An Outline Guide for the Care of Post-Operative Cardiac Patients. By Merle E. White, R.N. (Pp. 108+vii; illustrated. 48s.) Springfield, Illinois: Charles C. Thomas, Oxford: Blackwell Scientific Publications Ltd. 1961.

Persuasion and Healing. A Comparative Study of Psychotherapy. By Jerome D. Frank, M.D., Ph.D. (Pp. 282+xiv. 35s.) Baltimore, Maryland: The Johns Hopkins Press. London: Oxford University Press. 1961.

The Encyclopedia of the Biological Sciences. Edited by Peter Gray. (Pp. 1,119+xxi; illustrated. 160s.) New York: Reinhold Publishing Corporation. London: Chapman and Hall, Ltd. 1961.

Cell Function. An Introduction to the Physiology of the Cell and its Role in the Intact Organism. By L. L. Langley, Ph.D., LL.B. (Pp. 377+xii; illustrated. 60s.) New York: Reinhold Publishing Corporation. London: Chapman and Hall Ltd. 1961.

The Biology of Space Travel. Symposia of the Institute of Biology. No 10. Edited by N. W. Pirie, F.R.S. (Pp. 120+viii; illustrated. 25s.) London: The Institute of Biology. 1961.

Cerebral Palsy in Childhood and Adolescence. A Medical, Psychological and Social Study. Edited by J. L. Henderson, M.D., F.R.C.P.E. (Pp. 403+viii. 35s.) Edinburgh and London: E. and S. Livingstone Ltd. 1961.

Clinical Neurosurgery. Proceedings of the Congress of Neurological Surgeons held at Miami Beach, Florida, 1959. Volume 7. (Pp. 278+xvi; illustrated. 96s.) London: Baillière, Tindall and Cox. 1961.

Brompton Hospital Reports. A Collection of Papers by Members of the Staffs of the Hospitals for Diseases of the Chest—Brompton Hospital, London Chest Hospital, and of the Institute of Diseases of the Chest. Volume XXIX. Edited by W. P. Cleland, A. F. Foster-Carter, and K. F. W. Hinson. (Pp. 261+viii; illustrated. 15s.) London: Lloyd-Luke (Medical Books) Ltd. 1960.

Home Treatment in Injury and Osteoarthritis. By W. E. Tucker, C.V.O., M.B.E., T.D., M.A., M.B., B.Ch., F.R.C.S. (Pp. 80+viii; illustrated. 10s. 6d.) Edinburgh and London: E. and S. Livingstone, Ltd. 1961.

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PREVENTION OF INFECTION IN THE URINARY TRACT

Urinary infection has long been recognized as a common complication of operation on the lower urinary tract and drainage of the bladder by indwelling catheter. Even the simple passage of a catheter may cause infection. But opinions have differed on how much harm is done by the infections and how much effort should be made to prevent them. The truth seems to be that while most patients escape without serious harm an important minority suffer serious and sometimes fatal results, such as acute pyelonephritis and septicaemia. It is probable also that chronic pyelonephritis and recurrent cystitis sometimes originate in this way. Serious complications can be avoided only by preventing infection in all patients.

In the *Journal* this week Mr. G. W. Vause Greig reviews (page 543) the results of prostatectomy in a small provincial hospital. He stresses the danger of catheterization outside hospital, and records a high mortality among patients with retention who had been catheterized before admission. Mr. B. Lytton gives reassuring evidence (page 547) that routine cystoscopy carries little risk of infection, provided the instrument is properly sterilized. Mr. J. H. M. Pinkerton and his colleagues report (page 539) evidence of chronic pyelonephritis in 14% of patients reviewed five years after attacks of urinary infection in pregnancy. Infection in pregnancy doubtless originates in various ways. There is good evidence that catheterization is one of them.[1]

When a catheter has to be passed it is essential that it should be sterile. This is easily achieved by boiling or autoclaving. But infection may still result from re-contamination of the catheter by an inexperienced operator, or may be caused by organisms from the patient's introitus or urethra, which cannot be sterilized. Catheterization for diagnostic purposes therefore should be avoided when possible. Properly collected "mid-stream" specimens from female cases as well as males are suitable for bacteriological study.[1 2] Collection may be facilitated by using a simple tube to direct the flow of urine.[3] Indwelling catheters should be of plastic, since rubber may cause chemical urethritis, necessitating frequent changes of catheter and so increasing the liability to infection. For simple drainage, with no likelihood of obstruction by blood-clot the narrow-bore catheter described by N. Gibbon[4] is especially suitable.

Infection after prostatectomy and drainage by indwelling catheters may be caused by bacteria from the patient's own body or, more often, by cross-infection from others. But, whatever the source, the only important route of entry is the urethra (unless drainage by other channels creates other routes). Important studies carried out at Bristol by W. A. Gillespie and colleagues[5] showed that some infections started at operation and were caused by pathogens already present in the urethra, or more often were transferred from other patients on inefficiently disinfected cystoscopes. Most patients who escaped infection at operation succumbed afterwards to organisms which entered the bladder via the indwelling catheter, where they were conveyed by air bubbles rising up the drainage tube from an open bottle, or by irrigation with a bladder syringe to dislodge clots—a procedure which is difficult to perform aseptically. The possibility was also considered that bacteria proliferating in secretion between the catheter and the urethral wall might cause infection, but this route did not seem important in men whose bladders were drained for no longer than a week or so. (In females, however, because of the shortness of the urethra, it may be an important route when indwelling catheters are used after gynaecological operations.) These findings led the Bristol team to introduce special precautions in cases of prostatectomy by the transurethral and retropubic methods and drainage by indwelling catheters. The urethra was disinfected by instilling a solution of chlorhexidine. The disinfection of non-boilable cystoscopes and resectoscopes was improved by using aqueous or alcoholic solutions of chlorhexidine instead of mercury oxycyanide. Retrograde infection through the indwelling catheter was prevented by draining into a closed sterile vessel containing formalin, and a device was incorporated by means of which the bladder could be irrigated to dislodge clots without interrupting the closed drainage.[6]

The combined use of these methods reduced infection rates from 83% to 6% after prostatectomy and from 73% to 10% after simple drainage of the bladder for the relief of acute retention of urine. Further experience may suggest other technical modifications. It probably would be safer to disinfect

[1] Slade, N., and Linton, K. B., *Brit. J. Urol.*, 1960, 32, 416.
[2] Clarke, S. H. C., *Brit. med. J.*, 1960, 2, 1491.
[3] Leather, H. M., and Hutchings, M. T., *Lancet*, 1960, 2, 654.
[4] Gibbon, N., *Brit. J. Urol.*, 1958, 30, 1.
[5] Gillespie, W. A., Linton, K. B., Miller, A., and Slade, N., *J. clin. Path.*, 1960, 13, 187.
[6] —— Linton, K. B., Slade, N., and Mitchell, J. P., *Lancet*, 1958, 2, 608.
[7] Francis, A. E., *Proc. roy. Soc. Med.*, 1959, 52, 998.
[8] Paterson, M. L., Barr, W., and Macdonald, S., *J. Obstet. Gynaec. Brit. Emp.*, 1960, 67, 394.
[9] McLeod, J. W., *Lancet*, 1958 1, 394.

cystoscopes by "pasteurization"[7] than to rely on chemical disinfection. However, the results obtained by Gillespie and his colleagues were sufficient to show that infection is usually preventable and not, as has sometimes been thought, an inevitable accompaniment of urological procedures. The necessary precautions are simple in principle, but require detailed attention. The drainage and irrigation apparatus is best assembled and sterilized centrally, preferably in a sterile supply department. All this is easier to provide in a special unit than in a general ward which admits a few urological patients, and supports Mr. Greig's plea for specialized urological services.

Even when bacteria cannot be prevented from entering the bladder infection may sometimes be avoided by destroying them before they establish themselves. This approach was adopted by M. L. Paterson and his colleagues[8] for patients who required repeated catheterization after gynaecological operations. By instilling a small volume of dilute chlorhexidine solution into the bladder before the catheter was withdrawn they reduced the infection rate from 70% to 13.5%. This sort of judicious use of antisepsis is much preferable to the wholesale prophylactic administration of systemic antibiotics, for by breeding drug-resistant pathogens this is likely in the long run to cause more trouble than it saves.

One further point may be mentioned. The control of cross-infection is always facilitated by eliminating sources of the responsible organisms. Drainage of urine into closed vessels containing disinfectant contributes to this end, and should be employed whether the urine is infected or not. Some system of disinfecting urinals is also a worth-while measure in urological wards.[9]

MEDICAL AID TO DEVELOPING COUNTRIES

Under the chairmanship of Sir Arthur Porritt a conference was held at the Royal College of Surgeons towards the end of July to discuss ways and means of providing medical and surgical aid to underdeveloped countries—or, to use perhaps a more appropriate term, developing countries. The conference ended by agreeing to set up a working party to devise some form of co-ordinating machinery for this purpose, and the first step towards this was taken at the College of Surgeons on August 15 when a number of distinguished persons, with Sir Arthur Porritt as chairman, met as a nomination committee. The Committee considered the names of persons who would constitute the working party, and these will be made public in due course. The terms of reference of the working party are as follows: "To consider at a professional level the methods by which British medicine can contribute to the development of medical science and the medical services in the developing countries."

The two Government departments concerned in this venture will be the Ministry of Health and the new Department of Technical Co-operation. Sir Arthur's working party will be a completely independent body working in close co-operation with these two departments and the British Council. These are the bare bones of a skeleton which we hope will eventually acquire powerful muscles to put it into motion.

A number of informed speakers at the meeting in July ranged widely over the many problems turned up as a result of Sir Arthur Porritt's initiative, and however much they differed in detail they all agreed that something should be done, and done quickly. It was very much in Sir Arthur's mind that there should be a co-ordinated scheme throughout the Commonwealth, and indeed at one point he envisaged some form of Commonwealth Medical Service. Though this embodied his ideal of revivifying the influence of British medicine abroad, some thought the title might be a little misleading in its implications. What was wanted was a mechanism for co-ordination and co-operation, and it is to be hoped that the working party will provide this once it is set up.

The needs of different countries vary greatly, not least the needs of Great Britain, where, as it was pointed out at the Conference, some 50% of the registrar establishments in British hospitals are made up of doctors from Commonwealth countries. And one speaker urged that far greater attention should be paid to the distribution of doctors from overseas in British hospitals so that they could have the kind of training available in teaching hospitals. Another speaker pointed out that much of the emergency surgery in N.H.S. hospitals is done by foreign graduates—surgical registrars: this did not seem to him to be the best way of training them or dealing with emergency surgery in the U.K. The same speaker stressed what has been stressed before, that Britain has not enough doctors of her own. This, so it seems to us, is one of the great obstacles in the way of those who would wish to see going out from this country general service doctors to those developing countries desperately in need of trained medical and surgical aid. But in many of these areas, as various speakers stressed, what was wanted above all were the facilities and practice of preventive medicine. There is little doubt, too, that in many of the developing countries, with their new sense of national dignity, there will be an ever-increasing insistence on meeting their medical needs by trained doctors from their own people. And here it seems

that they would want, and one would hope would welcome, the teaching and the training that can be given on the spot by medical men from countries such as Britain. In other words, doctors from those advanced countries in the Commonwealth should go out and teach and train in the developing medical centres of the developing countries. There are the familiar difficulties of secondment and proleptic appointments, and Sir Arthur's working party will have to get to grips with the Ministry of Health and the Universities so that young teachers can go out without losing their place on the ladder at home. Probably much more could be done if senior men approaching the age of retirement imitated the example of the late Mr. Julian Taylor, when he went after retirement to teach surgery at Khartum. Whatever the difficulties, one may be sure that they will be overcome if the working party to be set up shares the energy, drive, and enthusiasm that Sir Arthur Porritt has shown in making this first important step.

TWENTY-FIVE HOURS IN SPACE

Compared with the scant information vouchsafed by Major Yuri Gagarin at a press conference he gave in London after his circuit of the earth, that given out by Major Herman Stepanovich Titov in a similar conference in Moscow, televised by the British Broadcasting Corporation, after his seventeen circuits on August 6–7, was informative indeed. But Major Titov had his questions sent up beforehand and read his replies from a prepared manuscript, whereas Major Gagarin was embarrassed by having to give his answers impromptu.

We learned this time, for instance, that Major Titov ejected himself from his capsule and made the final part of his descent by parachute, though he could have come down no less safely by staying in his ship. Moreover, he could have guided himself down to a landing at any stage of the flight, if the need arose. The difficult problem of re-entry into the atmosphere was surmounted by preliminary braking by rocket. The remaining deceleration could be accomplished by atmospheric friction without excessive *g* forces or excessive heat, though Major Titov relates that the air just outside became "luminescent" at this stage, its colour changing with altitude. The heat thus engendered in the outer skin would take time to filter through into the cabin atmosphere, and, according to recent estimates, would continue to do so after the landing if the cabin remained closed. Was this why Major Titov ejected himself?

The two Americans who made parabolic flights into space and back avoided this trouble, for the horizontal component of their velocity, which took them about 300 miles (473 km.) in a quarter of an hour, was only one-fifteenth of the 5 miles per second (8 km./sec.) which kept the Russians in orbit before they applied braking. This is as well, because on July 21 Captain Grissom, after descending to the Atlantic, stayed in his capsule for 11 minutes, which "were largely occupied in freeing himself from the straps that held him to his contour couch during the weightless period of the parabola."[1] As a safeguard against overheating in high-speed flight, Flight-Lieutenant J. Billingham, of the R.A.F. Institute of Aviation Medicine, has proposed and tried out a method of circulating cool air between the pilot's clothes and skin.[2] The temperature of Major Titov's cabin during the flight, whatever may have happened to it on the descent, is stated to have varied between 12° and 22° C. (54 and 72° F.), and the relative humidity between 55 and 75%. This means that the total amount of water vapour in the air did not remain constant but was greater at the higher temperature; otherwise the stated temperature range would have caused twice as big a change in relative humidity.

The carbon-dioxide content of the cabin atmosphere varied between 0.25 and 0.4%, Major Titov said; this, though about ten times the normal figure in fresh air, is generally accepted as the safe limit, and its rising to this level was probably allowed in order to keep down the weight of the absorption mechanism, whatever it may have been. Many chemical absorbers have been proposed for removing carbon dioxide and water vapour from a space cabin, and the estimated weight of them needed per man per day varies between 400 and 1,600 grammes, according to N. J. Bowman,[3] who recommends lithium oxide at 840 g./day. Disagreeing with all the others is Professor J. B. S. Haldane,[4] who once spent 48 hours in a miniature submarine with the carbon dioxide running as high as 3% and emerged without discomfort—at least, from that cause.

Oyxgen in the cosmonaut's cabin, at 25–27%, was not much above the normal 21%, and did not need to be, for we are told, rather surprisingly, that the air was kept at atmospheric pressure: surprisingly, in view of the great variety of pressures which have been proposed in the past, largely because of the alleged engineering difficulty of producing a completely air-tight compartment for retaining air at any pressure approaching its sea-level value of 760 mm. Hg. Cabin pressures recommended by various writers range from the absolute minimum of pure oxygen at

[1] Lear, J., *New Scientist*, July 27, 1961, **11**, 216.
[2] Billingham, J., in *The Biology of Space Travel*, ed. N. W. Pirie, 1961. Institute of Biology, London.
[3] Bowman, N. J., in *Realities of Space Travel*, ed. L. J. Carter, 1957. Putnam, London.
[4] Haldane, J. B. S., *J. Brit. interplanet. Soc.*, 1955, **14**, 87.
[5] Lansberg, M. P., ibid., 1960, **17**, 285.
[6] Ballinger, E. R., *J. Aviat. Med.*, 1952, **23**, 319.
[7] Calder, N., *New Statesman*, August 11, 1961.

160 mm. Hg up to an entire stock of oxygen at more-than-atmospheric pressure, which would be gradually reduced during the voyage as the gas was used up. Some experts would replace the nitrogen by helium to guard against the "bends" in case the cabin wall should spring a leak. But the mundane idea of subjecting the occupant to ordinary atmospheric pressure comes as something of a novelty to the student of astronautical literature.

Perhaps the most valuable physiological lesson of the flight is the discovery that weightlessness can be withstood for more than 24 hours (one can hardly call the period "a day and a night," for the sun rose on Major Titov seventeen times). The permanent sensation of falling, which so many writers forecast, has been condensed into a brief impression, at the onset of weightlessness, that his feet were uppermost; but in a few seconds, Major Titov said, his sensations reverted to "normal"—so much so that, when he looked out and saw the earth's globe overhead, he wondered momentarily what was keeping it up there.

The typical "manned satellite" design of the would-be astronautical engineer is a large wheel-like structure kept in rotation to provide centrifugal force as a gravity substitute for its occupants living in the periphery. But, as M. P. Lansberg[5] has pointed out, any rotation of the head round an axis different from that of the vehicle would provoke confusing impulses from the semicircular canals, since the two rotations would be superimposed. Major Titov's ship was presumably not rotating, since he could control its attitude: he had to, in order to bring the rocket jet round to the front before decelerating for his descent; but he spoke of receiving unpleasant sensations when making sharp movements of his head.

Was this, then, an example of the working of the Weber–Flechner law? According to this, the nerves register a change in the strength of a stimulus not according to the actual change, but according to the proportional change. So its application to the state of weightlessness would demand that a change from 0.01 *g* to 0.02 *g* would produce the same stimulus as a change from 1 *g* to 2 *g*. Moreover, a strict application of the law would lead to the absurd conclusion that a change from zero *g* to any other value of *g* would produce a stimulus of infinite strength. A more likely explanation is that, when the head is moved under normal gravity, the otoliths in the balancing organs of the inner ear are displaced in a direction compounded of the pull of gravity and the lag due to head movement. The eyes, whose involuntary motions are under the control of the otolith organs, have learned to compensate automatically for the head movements of which the otoliths have informed them. In the absence of gravity, however, the direction of displacement of the otoliths is entirely due to lag, but they do not "know" it; consequently wrong information is relayed to the eyes. Nevertheless, passengers submitted by E. R. Ballinger[6] to 20-second weightless periods in an aeroplane found that they could nod and shake their heads without ill effect. So it may be a matter of personal idiosyncrasy.

"The sanitation functioned well," according to Major Titov's interpreter, and there was no odour—in fact the air seemed purer than on the earth. His appetite in this bracing environment, however, was poor, and he attributes this to a combination of weightlessness and excitement, not to the toothpaste-like form in which his food was served up. He squeezed himself a dinner at 12.30 p.m., 3½ hours after take-off, and at 6.30 p.m. a supper, followed by bed. He was scheduled to sleep until 2 a.m., during his 7th to 12th circuits of the earth, but, after waking up more than once, finally overslept by 35 minutes, without, he asserts, having had any dreams. His ability to sleep so well under zero gravity appears to contradict a finding from an experiment in the United States in which a subject was first deprived of sleep for 48 hours and then taken up in an aeroplane and submitted to a short period of weightlessness during a parabolic "Keplerian trajectory." On being bedded down in the aeroplane he promptly fell asleep, only to wake up at the onset of the weightless period with a feeling that his limbs had "floated away" from him. But again, it was the sudden disappearance of weight, rather than its continued absence, that brought on a feeling not unlike that of Major Titov when his feet seemed to rise above him. As to that extra 35 minutes of somnolence in defiance of the official time-table, one can but agree with Nigel Calder[7] that "here was indolence in the Grand Manner; in the most expensive *wagon-lit* ever, the phlegmatic major snatched an extra ocean and continent of sleep."

LOCAL OR SYSTEMIC ACTION?

Dr. G. A. Stanton,[1] in a letter published in last week's *Journal*, raises an important point of principle in therapeutics. His argument derives from the suggestion in the paper by E. T. Knudsen and others[2] that the high concentrations of "penbritin" attained in the urine account for its success in treating infections of the urinary tract. Dr. Stanton denies that an action in the lumen of the urinary tract can be curative, and maintains that only a systemic action can achieve this. He pursues this argument mainly with reference to the intestinal tract, where, in his experience, sulphonamides of low solubility are much less useful in treating infections than such drugs as sulphadiazine and sulphadimidine, which are intended to be wholly or largely absorbed and to act

[1] Stanton, G. A., *Brit. med. J.*, 1961, **2**, 519.
[2] Knudsen, E. T., Rolinson, G. N., and Stevens, Shirley, ibid., 1961, **2**, 198.

systemically. If he is referring to the treatment of specific acute enteritis (*Salmonella*) or to bacillary dysentery, in which the bowel wall is deeply involved by either an inflammatory catarrh or actual ulceration, no one is likely to disagree with him: indeed, sulphadiazine was extensively used in preference to sulphaguanidine for this purpose, and the ordinary soluble sulphonamides were also popular for treating acute gastro-enteritis in infants. The indications for sulphonamides of low solubility, which remain in the bowel and are little absorbed, are the prophylaxis of intestinal infections (the object being to prevent the proliferation of any bacilli which gain access to the bowel) and, secondly, the general suppression of the intestinal flora, as in preparation for colonic surgery. Neither of these objects calls for any systemic effect.

With infection of the urinary tract there is the same choice between aiming at a systemic or a purely local effect, either by the selection of a drug or according to the dose of it prescribed. Dr. Stanton takes the view that to destroy bacteria in the lumen alone is useless—that only a systemic effect will serve. This is to deny that any urinary antiseptic in use before 1935, when the sulphonamides were introduced, had any therapeutic effect. It is nevertheless indisputable that both the ketogenic diet, the effect of which was to cause the urinary excretion of β-hydroxybutyric acid, and the much simpler administration of mandelic acid, which replaced the ketogenic diet, cured certain urinary-tract infections. Neither of these acids exists in the kidney parenchyma or other tissues in a concentration adequate for antibacterial effect. In patients in whom this treatment was successful it was enough to eliminate bacteria from the urine itself. When the tissues lining the urinary tract ceased to be bathed in a fluid teaming with bacteria they could look after themselves. The same may be said of the use of hexamine or of nitrofurantoin: the former is inert in the tissues and the latter attains antibacterial levels only when concentrated in the urine. Unfortunately not all urinary-tract infections can be dealt with so simply, and whether they can must obviously depend on what tissues are involved. The superficial involvement in a pure cystitis or even pyelitis responds to sterilization of the lumen: the deep involvement of the kidney in a true pyelonephritis obviously will not. The problem is to distinguish pyelonephritis, which calls for well-directed and sustained systemic treatment, from simple infection of the urinary tract proper, which can often be successfully treated by much simpler means. The diagnosis of pyelonephritis is not easily made except in its later stages, but long persistence and refractoriness to treatment are strongly suspicious of it.

LESS NOISE IN HOSPITALS

Recent inquiries have shown that noises in and around hospitals worry at least half of the patients, and the King Edward's Hospital Fund for London has published two reports on how to reduce this nuisance.[1] Last week a subcommittee, under the chairmanship of Miss M. B. Powell, of the Standing Nursing Advisory Committee of the Central Health Services Council, issued a report[2] which contains many practical suggestions for controlling noise in hospitals. For instance, twelve items of equipment are listed—from trolleys to meal trays—with advice on how each should be maintained and used so that noise is reduced to a minimum. The subcommittee recommends that hospitals should hold periodic inquiries on noise and that convalescent patients might be asked to keep records of the most bothersome noises.

The report mentions the well-known fact that many patients are disturbed by the admission of emergency cases at night and by the presence in the main wards at all times of very ill patients and of patients recovering from operations. It is therefore recommended that separate accommodation should be provided for these patients, and that if such accommodation is not available then patients should be prepared for emergency operations at night in casualty rather than in a main ward. In a letter published this week (p. 583), Mr. J. P. Stephens suggests that surgical patients from the waiting-list should also be admitted into separate cubicles in order to minimize the risks of staphylococcal infections. The case for more small wards and cubicles is thus strengthened on two counts—the control of noise and the control of infection.

FLEMING MEMORIAL FUND

An international appeal for contributions to the Fleming Memorial Fund was announced in March this year. In response to this some £350,000 has so far been raised—a long way short of the million pounds the trustees aimed at. This is certainly not a handsome response from a world-wide public which has gained such immense benefits from the discovery of penicillin; especially when the objects of the fund are considered. As was announced earlier this week, the Fund exists to commemorate Sir Alexander Fleming and his discovery of penicillin by raising money to provide assistance for "basic medical research anywhere in the world." Medical men could at least help by persuading some of their patients to send contributions to the Secretary to the Trustees, The Fleming Memorial Fund for Medical Research, 26 Upper Brook Street, London W.1.

The Trustees, however, are not waiting until their target has been reached before making funds available for research. It is hoped to make the first grants before the end of this year. Applications should be sent to the Secretary to the Trustees. Grants may be given to universities, research institutions, and individuals engaged in research, and to provide national and international fellowships. This is the kind of memorial that Sir Alexander Fleming would have liked best.

[1] See *Brit. med. J.*, 1960, 2, 1946.
[2] *Control of Noise in Hospitals.* Prepared by the Standing Nursing Advisory Committee of the Central Health Services Council. Ministry of Health, Savile Row, London W.1.

MAXIMUM PERMISSIBLE CONTAMINATION OF RESPIRABLE AIR AFTER AN ACCIDENTAL RELEASE OF RADIOIODINE, RADIOSTRONTIUM, AND CAESIUM-137

REPORT TO THE MEDICAL RESEARCH COUNCIL BY ITS COMMITTEE ON PROTECTION AGAINST IONIZING RADIATIONS

The Medical Research Council, at the request of the United Kingdom Atomic Energy Authority, has continued to consider the consequences of the release of radioactive material as a result of fires or other incidents at atomic energy establishments. The Council's Committee on Protection against Ionizing Radiations first reported[1] on the maximum permissible dietary contamination for iodine-131, strontium-89, strontium-90, and caesium-137, since it was considered that for the members of the public normally resident in the area affected, "ingestion of contaminated food would generally be the limiting source of hazard after any such accident" and that "intake by inhalation, or radiation from the exterior, would become of importance only in rather special circumstances."

The Committee has subsequently reported[2] on the problem of exposure from the exterior—namely, from external sources of beta and gamma radiation. The present report now deals with the problem of exposure from radioactive material which is inhaled during the passage of a cloud of such material. As in the case of the ingestion and the external radiation hazards, the Committee has considered what the biological consequences of exposure might be, so that appropriate administrative action can be planned.

The persons most at risk are likely to be those who are working or residing in the immediate neighbourhood of the site of an accidental release of radioactive material. It should be noted that such persons may also be exposed simultaneously to external radiation of relatively short duration during the passage of the same cloud of radioactive material, and subsequently to external radiation from material deposited from the cloud and to internal radiation from foodstuffs contaminated thereby. Consequently, the doses which their various body organs might receive from inhaled materials will determine the acceptable amount of radiation from the other sources mentioned.

The Council's Protection Committee now recommends certain levels of radioactivity in the air that should, if possible, not be exceeded. In deciding upon these levels the Committee has used the fullest information available at the present time, but it is necessary to stress that knowledge of the metabolic behaviour and effects of ionizing radiation is continually increasing, and that the subject of permissible doses is constantly under review.

In its previous reports on emergency exposures the Committee has referred to the many factors which have to be balanced in specifying the acceptable levels of emergency exposure, such that it is unlikely that any short-term or long-term effects will be observed. It again stresses that doses which are described as acceptable do not represent levels below which there is no effect whatsoever and above which there will necessarily be serious consequences. This should be borne in mind by the responsible authority when assessing the risks of evacuating people relative to the risks of permitting doses in excess of those recommended.

In deciding upon the acceptable doses, the Committee has had in mind the small probability that the same persons would be involved in more than one emergency. However, the levels have been set sufficiently low that a second exposure after a period of some years should not give rise to undue concern.

The present proposals may be compared with the most recent recommendations of the International Commission on Radiological Protection (I.C.R.P.),[3,4] but in so doing it should be appreciated that the Commission has not so far made any specific recommendations concerning emergency doses for the general population. It has, however, noted the Medical Research Council's report[1] on maximum permissible dietary contamination, and considers[4] that this report "constitutes a useful and sound approach to the subject." The I.C.R.P. recommendations refer principally to the long-continuing exposure of persons in the group that is occupationally exposed to ionizing radiations and are intended to limit both the short-term and the long-term effects to acceptable levels. Reference is, however, made to the "emergency" exposure of persons in this group. These aspects are discussed below in relation to the present proposals.

Recommendations

In its report on dietary contamination after a nuclear reactor accident the Committee was able to point to three main effects which required assessment—namely, irradiation of the thyroid gland by radioiodine, of the bone and bone-marrow by radiostrontium, and of the whole body by radiocaesium. In making its recommendations for the maximum permissible contamination of foodstuffs, principally fresh milk from cows grazing contaminated pastures, the Committee took into account the likely sequence of rise and fall of food contamination consequent on the deposition of radioactive material on herbage and its subsequent removal by radioactive decay and weathering. It was envisaged that the sequence, and therefore the period of uptake of radioactive materials by human beings, might last days or weeks. By contrast, the risks of inhaling radioactive materials after a nuclear reactor accident will be of very short duration, lasting a matter of hours. In consequence of this, the variation with time of the radiation doses delivered to the appropriate body organs, as well as perhaps of the distribution of the radioisotopes in the organs, will be different in the two cases.

It is very possible that, at the maximum levels of dose previously recommended, these two factors have little biological importance, although direct experimental evidence is lacking. In view of this and of the fact that the fission products of greatest importance are once again radioiodine, radiostrontium, and radiocaesium, the Committee considers that the values previously recommended for the maximum permissible dose or dose-rate to critical organs after the absorption of these radioisotopes from the diet should also be applicable for their inhalation during an emergency. Thus the maximum intakes of radioiodine proposed for various ages correspond to a total thyroid irradiation of 25 rads; the intakes for ^{89}Sr and ^{90}Sr correspond to a total of 15 rads and an annual rate of 1.5 rads a year respectively, at sites of highest concentration in bone, and the ^{137}Cs intake gives a total dose of 10 rads to the whole

body. In addition, the intakes of these radioactive isotopes have to be considered in relation to maximum total lung dose, for which the proposed value is 15 rads.

The recommended values for the total intakes at different ages of ^{131}I, ^{89}Sr, ^{90}Sr, and ^{137}Cs, into the body via the lung, and for the corresponding time integrals of the concentrations of these radioisotopes in air, are shown in the Table. Where there is a dose contribution from other isotopes of iodine and from ^{132}Te (the parent of ^{132}I), the values given for ^{131}I should be reduced by a factor of 2, though in certain rare circumstances, for instance, inhalation shortly after a critical excursion with fissile materials, the values might have to be reduced by a factor of 10.[5]

It should be noted that the values shown in the Table refer to the intake of each radioisotope separately. Where more than one of the isotopes mentioned irradiate the same organ, the doses which they contribute are additive and therefore necessitate corresponding adjustment of the permissible intake of each isotope. For example, the intake of ^{137}Cs, which results in the irradiation of the whole body, automatically reduces the permissible intake of all other radio-elements. Similarly, where the intake consists of both ^{90}Sr and ^{89}Sr, their separate intakes must be reduced below the levels recommended in the Table, according to the proportion of each which is present in the atmosphere.

The recommended intakes, either separately or collectively as just described, will not result in an average dose to the lung as high as the maximum level of 15 rads referred to above, except in the unlikely event of an intake of ^{137}Cs in the form of insoluble particulate material.

It will be noted that the values are always lower for children than adults, and no doubt this will be taken into account by those persons responsible for deciding at what stage, if any, to evacuate the public during any emergency.

The recommended intakes for adults may be compared with the values derived from the recommendation by the I.C.R.P.[6] for emergency exposures of adult occupationally exposed persons—namely, that " the total intake of radioactive materials during the emergency period should not exceed the amount that would result from intake for one year at the maximum permissible levels for occupational exposure to such radioactive materials permitted by the 1959 report of Committee II." The values so derived—namely, about 22 μc of ^{131}I, 75 μc of ^{89}Sr, 0.75 μc of ^{90}Sr, and 150 μc of ^{137}Cs—are all very similar to those shown for adults in the Table.

Maximum Permissible Total Intakes and Time Integrals of the Concentrations in Air of ^{131}I, ^{89}Sr, ^{90}Sr, and ^{137}Cs for Persons of Different Ages Following a Nuclear Reactor Accident

	Birth		6 months		1 year		Adult	
Radio-isotope	Total Intake (μc)	Time Integral of Concentration ($m\mu$c hour/litre)	Total Intake (μc)	Time Integral of Concentration ($m\mu$c hour/litre)	Total Intake (μc)	Time Integral of Concentration ($m\mu$c hour/litre)	Total Intake (μc)	Time Integral of Concentration ($m\mu$c hour/litre)
^{131}I *	0·88	8·8	0·88	3·5	1·1	3·3	20	24
^{89}Sr	2·8	28	5·5	22	8·3	25	83	100
^{90}Sr	0·028	0·28	0·057	0·23	0·085	0·26	0·85	1
^{137}Cs	8	80	19	76	22	66	150	180

* Where there is a dose contribution from other iodine isotopes and ^{132}Te, the values for ^{131}I should be reduced by the factors indicated in the text.

Comments on the Recommendations

The amount of radioactive material inhaled and subsequently retained by any individual during the passage of the radioactive cloud will depend on certain factors such as breathing rate, which may vary considerably. For example, the breathing rate will depend on the state of activity of the individual and will be lowest when he is at rest. The volume of air breathed daily (24 hours) by an adult has been taken to be 2×10^4 litres,[6] comprising 1×10^4 litres during the eight-hour work day and 1×10^4 litres during the remaining 16 hours when not at work. It has been assumed that, on average, this will correspond to an inhalation of about 830 litres/hour at any time. The corresponding assumed averages for children are about 100 litres/hour, 250 litres/hour, and 330 litres/hour at birth, 6 months, and 1 year respectively.

The amount of material which subsequently reaches the blood-stream, and consequently the appropriate organ of the body, after inhalation depends not only on the metabolic behaviour of the material but also on its physico-chemical nature. As regards particulate material, the physico-chemical characteristics which have to be taken into consideration are the shape, size, mass, and nature of the particles as well as their solubility.[7-12] Furthermore, there is some evidence that the concentration of dust in the inhaled air may also affect the rate of elimination of particles from the lung.[13] A further complicating feature is that some soluble radioactive materials may be absorbed on to highly insoluble particulate matter, thereby modifying their subsequent fate in the body.[14] It will thus be clear that the pattern of uptake and retention of radioactive materials following their inhalation will vary considerably according to the nature and scale of the accident.

At present our knowledge of the conditions to be expected in any particular accidental release of radioactive material is very limited. The Committee has, however, made recommendations which, in the light of present knowledge, are believed to give an adequate margin of safety. It is considered that, for the isotopes of iodine and caesium, 75% of the inhaled activity may reach the blood and that, for the strontium isotopes, the corresponding figure is 40%. Both values are the same as those recommended by the I.C.R.P.

Radioiodine

The Committee considers that the maximum intake of radioactive iodine should be such that the mean radiation dose to the thyroid gland could not exceed 25 rads. After any intake of radioiodine into the body, the dose to the gland will depend upon the thyroid size and the uptake from the lung at different ages. The mass of the gland has been taken to be 1.8 g. from birth to 6 months, 2.2 g. at age 1 year, and 25 g. in the adult, the uptake of iodine from the blood to the thyroid falling from 50% in childhood to 30% in adult life.[1] The dose will depend also upon (*a*) the average energy imparted to the thyroid after each disintegration of the radioisotope concerned, (*b*) the radioactive decay period, (*c*) the rate of uptake into the gland, and (*d*) the subsequent rate of biological elimination. Biological elimination from the thyroid is slow and it may be neglected in comparison with the decrease in thyroid activity due to radioactive decay for any of the isotopes concerned. Uptake into the gland takes place fairly rapidly, half of the maximum gland content being reached in a few

hours. Accordingly, it is an important consideration in the calculation of dose only when the isotope concerned has a relatively short radioactive half-period. It may be neglected, for example, in the case of ^{131}I, which has a radioactive half-period of about eight days and, except in special circumstances referred to later, this is the most important radioisotope of iodine requiring assessment.

The average energy imparted to the thyroid per disintegration of ^{131}I is 0.19 MeV,[15] due to the beta rays, together with a small contribution from the absorption of the gamma-ray component, which, in the adult thyroid, amounts to about 0.04 MeV, but will be less for the smaller thyroids of children. The total energy has, however, been taken as 0.23 MeV for all ages. The amount of ^{131}I entering the blood which will result in a thyroid dose of 25 rads is then found to be 0.66 μc, 0.81 μc, and 15.3 μc at birth to 6 months, at 1 year, and in the adult respectively. Assuming that 75% of any ^{131}I inhaled reaches the blood, the corresponding permissible activities in the inhaled air are therefore 0.88 μc, 1.1 μc, and 20 μc. The breathing rates at different ages have already been given above, and the maximum permissible time integrals of the concentrations of ^{131}I in the air are therefore 8.8 mμc hour/litre at birth, 3.5 mμc hour/litre at 6 months, 3.3 mμc hour/litre at 1 year, and 24 mμc hour/litre for the adult.

In most instances the release of ^{131}I will be accompanied by releases of other isotopes of iodine and of ^{132}Te, the parent of ^{132}I. In assessing the dose contributions from these isotopes relative to ^{131}I, consideration has to be given to certain factors such as: (*a*) Type of event—for example, reactor excursion or a fire; (*b*) time for which the reactor has been in operation; (*c*) period of time between the event and the occurrence of inhalation; (*d*) extent to which ^{132}Te is released into the atmosphere relative to the iodine isotopes; and (*e*) variation of rate of uptake from the blood into the thyroid gland, which may depend on age. In the circumstances most likely to occur in a reactor accident, the presence of the various iodine isotopes and ^{132}Te will increase the dose contributed by ^{131}I alone by a factor of 1.5–2, and the maximum permissible total intakes and time integrals of the concentration in air for ^{131}I which are listed in the Table should therefore be reduced by a factor of 2. In the unlikely event of a criticality excursion with fissile materials and of inhalation taking place shortly after the event, the dose contributed by the iodine isotopes and ^{132}Te may be as much as 10 times higher than that by ^{131}I. The figures given in the Table may therefore need reducing when special circumstances necessitate this.

Radiostrontium

The Committee recommends that the inhalation of radiostrontium should be limited so that sites of maximum concentration in bone receive a maximum total dose of 15 rads from ^{89}Sr and a maximum annual dose of 1.5 rads from ^{90}Sr.

After any intake of radiostrontium into the blood the maximum radiation dose or dose-rate received by any site in bone will depend not only upon the average energy imparted to the tissues following each disintegration of the radioisotope and the rate of radioactive decay but also upon (*a*) the concentration of the radioisotope at that site, (*b*) the rate at which the deposit is laid down, (*c*) the rate of elimination, and (*d*) the linear dimensions of the deposit if these are less than the maximum range of the beta particles concerned. All of these four factors depend in a complicated way upon the rate of skeletal growth and remodelling, and they will vary considerably according to the age of the individual concerned. None of them is known with any precision for humans, particularly for young children. The rate of entry of radiostrontium into the blood from the lung may also vary in a complicated manner, depending upon the site and type of the deposition in the lung as outlined above. However, after reviewing the available evidence, the Committee is of the opinion that the radiation dose at any site of maximum concentration may be assumed to be about five times greater than that which would be obtained if all the isotopes were distributed uniformly throughout the whole skeleton.[16–18]

The skeletal weight has been taken to be 7 kg. for the adult and about 30 times, 15 times, and 10 times less than this for the child at birth, 6 months, and 1 year respectively. A factor 0.3 has been assumed for the fraction of the isotope in the blood which will be deposited in bone. This is the same as that recommended by the I.C.R.P. and, together with the factor 0.4, mentioned above (for the fraction of the inhaled material which reaches the blood), gives an overall factor of 0.12 for the fraction transferred from the inhaled air to bone. The average energy imparted to bone after each disintegration of ^{89}Sr has been taken to be 0.55 MeV and the radioactive half-period to be 50.5 days.[6] Assuming no biological elimination of the isotope from the bone, the amounts of inhaled ^{89}Sr which will give a total dose of 15 rads at sites of maximum concentration are therefore 2.8 μc, 5.5 μc, 8.3 μc, and 83 μc respectively at birth, at 6 months, at 1 year, and for the adult. For ^{90}Sr the average energy per disintegration is 1.1 MeV[6] and the corresponding amounts of inhaled ^{90}Sr which will give a dose rate of 1.5 rads a year initially at a site of maximum concentration are 0.028 μc, 0.057 μc, 0.085 μc, and 0.85 μc.

If we adopt the breathing rates given above for the different ages, the permissible time integrals of the concentrations of ^{89}Sr in air are, therefore, 28 mμc hour/litre at birth, 22 mμc hour/litre at 6 months, 25 mμc hour/litre at 1 year, and 100 mμc hour/litre for the adult. The corresponding values for ^{90}Sr are about 100 times less.

Caesium-137

The Committee considers that the maximum intake of radioactive caesium should be such that the mean dose to the whole body could not, in the most unfavourable case, exceed 10 rads.

In the absence of any precise information on the distribution of radioactive caesium in the body, it has been assumed, in accord with the views of the I.C.R.P., that it will be uniformly distributed throughout the body tissues. As in the report on dietary contamination,[1] the mass of the body is taken to be 3.7 kg. at birth, 8.8 kg. at 6 months, 10 kg. at 1 year, and 70 kg. in the adult. It has been assumed that 75% of the inhaled ^{137}Cs enters body fluids and that its half-period in the body is 20 weeks.[19 20] There is some evidence, however, that a fraction will be eliminated more rapidly than this,[21] giving a resultant dose which will be somewhat lower than that assessed on the basis of the 20-week period. Taking the average energy imparted

to tissues after each disintegration of ^{137}Cs to be 0.59 MeV,[6] the total activities in the inhaled air which will give a mean dose of 10 rads to the whole body are 8 μc at birth, 19 μc at 6 months, 22 μc at 1 year, and 150 μc for the adult.

Using the breathing rates given above for the different ages, the corresponding maximum permissible time integrals of the concentrations of ^{137}Cs in air are therefore 80 mμc hour/litre, 76 mμc hour/litre, 66 mμc hour/litre, and 180 mμc hour/litre.

Dose to the Lung

The average dose received by the lung will depend upon the average time which the material spends in lung tissues before its transfer from there to other parts of the body. The dose will increase, therefore, with the degree of insolubility of particulate material. Following the views expressed by the I.C.R.P.,[6] it has been assumed that, in the case of "insoluble" material, one-eighth of that inhaled will be retained deep in the lung and subsequently eliminated with a half-period of 120 days. The mean dose to the lung also depends upon the mass of the lung and upon the effective energy of the radiation emitted by the radioisotope concerned. The mass of the lung has been taken to be 50 g. at birth, 110 g. at 6 months, 140 g. at 1 year, and 1,000 g. in the adult.[6 22]

The values for the effective energies which are recommended by the I.C.R.P. for adult lungs are 0.30 MeV for ^{131}I, 0.55 MeV for ^{89}Sr, 1.1 MeV for ^{90}Sr, and 0.41 MeV for ^{137}Cs. If we assume these to be equally applicable at all ages, this will lead in the case of the gamma emitters ^{131}I and ^{137}Cs to an overestimate of the calculated average dose for children, due to their smaller lungs. Ignoring this factor, the average radiation dose to the lung resulting from the total intakes recommended in the Table are as follows. For ^{131}I the values are 0.37 rad at birth, 0.17 rad at 6 months, 0.16 rad at 1 year, and 0.42 rad in the adult. For ^{89}Sr the corresponding values are 10 rads, 9 rads, 11 rads, and 15 rads; for ^{90}Sr they are 0.67 rad, 0.62 rad, 0.73 rad, and 1.0 rad; and for ^{137}Cs they are 70 rads, 78 rads, 71 rads, and 67 rads. Thus in the cases of insoluble ^{131}I, ^{89}Sr, and ^{90}Sr the recommended maximum dose of 15 rads to the lung will not be exceeded at the maximum permissible intakes recommended in the Table. In the case of ^{137}Cs the chance of it appearing in an insoluble form is so low as to make it extremely unlikely that this will dominate the figures presented in the Table.

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To-day's Drugs

With the help of expert contributors we publish below notes on a selection of drugs in common use.

"Soluvone" (Distillers Company (Biochemicals)).

Composition.—Soluvone is a product which combines 500,000 units of penicillin (sodium salt) *B.P.* and 0.5 g. streptomycin sulphate *B.P.* for injection.

Therapy.—The subject of combination chemotherapy is one on which there has been much controversy. Though there are arguments in favour of combining antibiotic preparations, and conditions where this practice is desirable, it may be said in general that antibiotics are best given separately. Combinations of antibiotics are indicated in hospital practice for a few selected conditions, and the antibiotics and their dosage are determined on the results of bacteriological sensitivity tests and the severity of the illness. There is, therefore, little if any place in hospital practice for a preparation combining two antibiotics in fixed dosage.

In general practice, even where laboratory tests may not readily be available, it is still best to use antibiotics separately. The combination of penicillin and streptomycin appears, however, to be used widely. While blind combination therapy cannot be commended, it is possible that on occasions there may be valid reasons for this in the treatment of some conditions—for example, the mixed infections of acute exacerbations of chronic chest disease.

If such therapy is given, the dangers must be appreciated. Adequate dosage of each drug is necessary to prevent the development of resistant strains, and combined preparations have an inflexibility of dosage which may lead on the one hand to development of resistant organisms or on the other hand to toxic effects. If the patient fails to respond to this therapy, bacteriological investigation must be instituted before further blind antibiotic treatment complicates the picture even more.

Side-effects.—The side-effects are those of penicillin and streptomycin. The main dangers are of allergic reactions, skin rashes, and damage to the auditory nerve.

Contraindications.—The preparation is contraindicated where there is known sensitivity to either antibiotic or evidence of renal disease. In all cases it is essential that the diagnosis is known, and it is preferable that the organisms have been identified and antibiotic sensitivities determined.

N.H.S. Basic Price.—Single-dose vials, five for 8s. 9d.; five-dose vials, ten for 66s. 8d. (each 6s. 8d.).

Correspondence

Because of heavy pressure on our space, correspondents are asked to keep their letters short.

R.C.S. Meeting in Sheffield

SIR,—I am grateful to you for allowing me to use this opportunity of bringing to the notice of the profession that the College is holding its annual meeting this year on November 24 and 25, in Sheffield.

As you know, the College has recently adopted the policy of holding meetings from time to time in provincial centres, and the last of these was held in Cardiff in 1958. The purpose of the council in holding these meetings is to bring the College closer to its provincial fellows and members and to enable them to take part in some of its activities. The council is particularly anxious that members of the College shall join us at this meeting, and any other diplomates will of course be very welcome. Fellows have already been notified individually.

The meeting will commence with a subscription dinner on Friday, November 24, in the Cutlers' Hall. Tickets for the dinner (£2 12s. 6d. each) can be obtained from the secretary of the College, but numbers are limited, and early application is necessary. Fellows and members may apply to bring male medical or non-medical friends as personal guests.

On Saturday, November 25, the morning will be devoted to scientific exhibitions and films at the new teaching hospital, followed by a fork lunch, kindly given by the board of governors of the United Sheffield Hospitals in the refectory of the university. In the afternoon, at 2.30 p.m., the statutory annual meeting of fellows and members will be held in the Firth Hall, and this will be followed by the conferment of the honorary fellowship of the College on Sir Howard Florey, P.R.S., who will afterwards deliver the Arthur Hall Lecture (under the auspices of the Arthur Hall Trustees).

The council hopes that this meeting will prove to be as successful an event as was the meeting in Cardiff, and we trust that our colleagues in Yorkshire and the Midlands will make a special effort to attend.—I am, etc.,

ARTHUR PORRITT,
President,
Royal College of Surgeons of England.

London W.C.2.

Pulmonary Tuberculosis and Pregnancy

SIR,—In putting forward their views on the management of pulmonary tuberculosis during pregnancy (July 8, p. 78), it must be pointed out that Drs. Ronald B. Pridie and Peter Stradling write with the authority of adult chest physicians but not of paediatricians. Statements such as "breast-feeding can be allowed by all parents who prove bacteriologically negative," or "patients found infectious early in pregnancy can often be rendered non-infectious in time to suckle their infants," give the unfortunate impression that breast-feeding is desirable and safe under these circumstances for both mother and child. Since the authors provide no evidence as to the fate of the babies in their series, this may well be unintentional.

From the paediatrician's standpoint, the exposure of a newborn baby to either parent with recent active pulmonary tuberculosis is dangerous and wholly unjustifiable. The newborn infant is highly susceptible to the tubercle bacillus, and it is generally accepted that a single bacillus is enough to produce a fatal infection in a baby. In this respect, the experience of Kendig and Rodgers[1] is of considerable interest. The infant of one of their patients developed tuberculosis after only one single, inadvertent breast-feed; another baby who had been allowed to remain in the same room as its sputum-positive mother for 12 hours after birth developed widespread pulmonary tuberculosis 19 days later. Only last year Kendig[2] published a further report on the fate of 83 infants born of tuberculous mothers. In 41 of these the mother's disease was supposedly inactive and the sputum negative for tubercle bacilli, yet 20 of the 41 babies acquired a tuberculous infection and three of the babies died of tuberculous meningitis. In contrast, all 12 babies in the series who had been separated from their mothers at birth and given B.C.G. vaccination were completely protected.

In this country the incidence of tuberculosis in the newborn is fortunately rare, but this is probably a measure of the success of the routine precautions followed by most paediatric and obstetric units. The current teaching briefly is that where a mother has, or has recently had, active disease sufficient to warrant chemotherapy (other than prophylactically), the mother must be isolated from the lying-in ward and nursery, and her baby must be separated from her (or, for that matter, any other suspect relative) until such time as effective B.C.G. vaccination is evidenced by a positive tuberculin reaction. Since the period of separation rarely exceeds six weeks, most parents will accept these precautions in the interests of the baby, except when they have been given conflicting advice by their chest clinics. Closer co-operation between the chest physician and paediatrician is clearly desirable to avoid this confusion.—We are, etc.,

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Jaundice and Deafness

SIR,—In your annotation (July 15, p. 162) concerning the above subject you made the following statement: "Injections of albumin have been used experimentally to lower the [serum] bilirubin [level] in jaundiced rats, but these investigations are not yet advanced enough for application to clinical medicine." I am writing to correct this statement, because the use of albumin infusions in jaundiced neonates may represent a significant advance in treatment.

At the meeting of the American Pediatric Society in Atlantic City, N.J., in May, 1961, Drs. Odell and Cohen, of Johns Hopkins University, reported on "Albumin Priming in the Management of Hyperbilirubinemia by Exchange Transfusion." They had measured the amount of bilirubin removed by exchange transfusion from three groups of jaundiced infants. Comparing the results in a series of 18 infants treated only by exchange transfusions with those obtained in 12 infants who were given one gramme of albumin per kg. of birth weight intravenously as 25% salt-poor albumin solution one to two hours prior to the exchange transfusion, the authors found that an average of 41% more bilirubin was

removed in the first exchange transfusion from those infants who had been "primed" before the exchange.

In the discussion following this paper it was reported that similar good results had been obtained by a group of physicians in Montreal. No doubt details of these observations will soon be recorded more fully. The basis for this method of treatment appears to be that the intravenous administration of concentrated human albumin to jaundiced infants is frequently associated with a significant *elevation* of the serum bilirubin concentration, presumably because bilirubin is drawn out of the tissues into the plasma. This finding had suggested that the removal of the bilirubin from infants by exchange transfusion might be enhanced if albumin was given previously.

It should be noted that this method of treatment may be contraindicated whenever the infant presents signs of heart failure, because the intravenous administration of albumin causes an increase in the infant's blood volume.—I am, etc.,

Department of Paediatrics, University of British Columbia, Vancouver, Canada. H. G. DUNN.

Beds for the Chronic Sick

SIR,—The difficulty of obtaining admission for an old person to hospital is well known to every general practitioner. The position is also recognized, or has been recognized, by Parliament, as in a debate on March 6, 1953, there was general agreement in approving a resolution to the effect that additional beds for the chronic and aged sick should be provided. It was further said in this debate that "this problem is probably the biggest challenge to the Welfare State in magnitude and the speed with which it is growing. It is one which can make or break the overall programme and the idea behind the Welfare State."

The census of 1951 showed that 11% of the population were in the pensionable group, and it was forecast that 20 years from that time this proportion would have risen to 16%. The recent census will no doubt show how accurate was this forecast. Thus we have an ever-increasing number of older people in our community for whom medical provision must be made.

Since 1950 geriatric units have been established in many parts of the country. These units provide beds basically of two types—those for the active treatment and rehabilitation of patients, and those providing long-term nursing which are usually described as "chronic beds." Whilst I do not agree with the use of this latter term, it is convenient to refer to it for the purpose of this letter.

Prior to 1929 municipal hospitals had large numbers of chronic-sick beds, but following the change in administration at that time specialized departments were established, usually by taking over wards rather than by building additional beds. Since 1948 this tendency has been accelerated and more chronic beds have been lost to the increasing demand for acute beds. The hospitals for mental diseases are now following the same pattern, and are excluding long-stay patients over the age of 60 years. It is said that these patients should be accommodated in geriatric wards.

We are thus in a position when the need for geriatric beds is greater than ever before, and will go on increasing. The demand has been met to some degree by our increasing use of specialized geriatric units where many patients previously considered to be chronic are rehabilitated, but there remains the group with degenerative changes for whom nothing but nursing is possible. These patients occupy hospital beds for varying periods of time and constitute a block in the discharge system of a hospital. It is probably true to say that all hospitals in this country have some acute beds blocked by chronic patients awaiting either transfer or death. The geriatric unit is in a difficult position in that demand for the admission of a patient at home who is abandoned, or needing urgent care for medical or social reasons, must take priority over a patient who is already receiving such care in hospital. An increased demand from the general population via the general practitioner will mean less transfers from the acute beds in the hospitals.

Adequate provision of long-stay beds will provide more accommodation for the care of the *acute* sick. From a cost point of view a long-stay bed can be built for approximately £1,500, whereas the provision of an acute bed costs more than twice that sum.

The problem of staff recruitment also requires attention. Nursing staff are in short supply throughout the whole of the hospital service, and it is inevitable that the majority will choose more dramatic aspects of nursing rather than work in a long-stay ward with patients who are often difficult and at times offensive. It is indeed fortunate that some women have a calling for this form of work. These chronic wards are, however, often the "Cinderella" of the hospital world, being put into accommodation which has been left over by other departments and being at the end of the queue for hospital development. Is it not time that new, purpose-designed units were built for the care of the chronic sick, planned on modern lines and giving consideration to amenities for the staff? This policy would result not only in more beds being provided and staffed for the aged sick, but would liberate beds for the young sick.—I am, etc.,

Hale, Cheshire. J. M. GREENWOOD.

Cortical Mastoidectomy

SIR,—In view of our interest in the pathology of middle-ear cleft infections we are prompted to comment on some of the points raised by Mr. R. S. McAlary in his paper entitled "Cortical Mastoidectomy is Still Necessary" (June 24, p. 1802) and by Mr. S. Silbermann in his letter (July 8, p. 109).

From our observations on the bacteriology and histopathology of "failed antibiotic cases" attending the Royal National Throat, Nose and Ear Hospital, we are led to the conclusion that, while there is a definite case for conservatism in some, there is an equally definite case for surgery in others. We would agree with Mr. Silbermann that a further course of penicillin, given parenterally, will often achieve a satisfactory result when oral antibiotic treatment has failed. Conversely there are a number of patients who are referred to hospital at a stage when further antibiotic treatment alone would seem to be inadequate, as illustrated by this case.

W. S., a child of 5 years, was admitted with a history of discharging left ear for four weeks, in spite of treatment with "ledermycin" (demethylchlortetracycline) and achromycin. On admission there was a profuse purulent discharge from the ear, together with some mastoid swelling and tenderness. *X*-rays showed clouding of the mastoid cells. Cortical mastoidectomy was performed, and the mastoid cells contained pus from which *Streptococcus pyogenes* was

grown in pure culture, sensitive *in vitro* to all antibiotics tested including tetracycline.

Histology of bone-chips (76/61) showed cellular mastoid bone with widespread destruction by inflammatory granulation tissue. Some of the cells were lined by infected mucosa showing columnar metaplasia. Much pus was present, together with fibrous granulation tissue and recently formed trabeculae of new bone (Figs. 1 and 2).

FIG. 1.—Mastoid cell filled with purulent necrotizing granulation tissue causing bone absorption. (H. and E. ×43.)

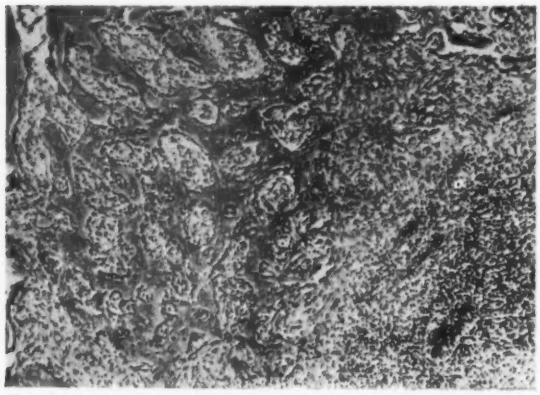

FIG. 2.—Newly formed trabecular bone (note rows of osteoblasts) replacing fibrous granulation tissue in another mastoid cell of the same specimen. (H. and E. ×38.)

The patient was given a course of intramuscular crystalline penicillin and discharged 10 days after operation.

It is difficult to believe that the pathological processes observed in the mastoid bone-chips from this case would have been arrested by further administration of antibiotics alone.

Of 770 mastoid bone-chip specimens submitted for histological examination during the period 1953–6, the great majority were from patients with chronic infections of the ear, but in 38 cases the features of acute or subacute mastoiditis were present.[1 2] Similar changes—that is, bone necrosis and the formation of fibrous granulation tissue and trabecular new bone—were observed in the bone-chips from a further 21 cases undergoing cortical mastoidectomy since that period. The similarity between these appearances and those described by Stewart[3] indicate that the introduction of antibiotics has not resulted in a fundamental change in the pathology of otitis media.

Since biopsy specimens obviously cannot be taken, the decision to operate must be made on clinical grounds, but we would say that, in the cases of acute mastoiditis examined by us, this decision was justified by the subsequent pathological findings.—We are, etc.,

I. FRIEDMANN.
A. L. JEANES.

Department of Pathology,
Institute of Laryngology and Otology,
London W.C.1.

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[1] Friedmann, I., *J. clin. Path.*, 1956, **9**, 229.
[2] —— *Ann. Otol. (St. Louis)*, 1959, **68**, 57.
[3] Stewart, J. P., *J. Laryng.*, 1928, **43**, 689.

Electric Convulsion Therapy

SIR,—I found Dr. W. E. R. Mons's observation (July 29, p. 307) of increased tolerance of thiopentone anaesthesia during a course of electroplexy of interest, particularly since two patients recently described to me how, toward the end of their course, they had remained conscious and had to bear the unpleasant effects of the muscle relaxant before being concussed.

Exposure to sedative drugs was, in these two cases, too brief to be explained in terms of drug tolerance alone, and it would seem that the changing clinical state of the patient is the important factor. It is known that acute psychosis decreases tolerance to sedative drugs,[1] and one would therefore expect recovery to be associated with greater resistance to thiopentone. Temporary "brain damage" induced by electroplexy may in some cases offset this, since organic disturbance increases susceptibility to sedation. Personality factors, notably extraversion–introversion and neuroticism (Eysenck), are also important, and one would predict that the introverted neurotic or dysthymic individual would, on recovery from a psychosis, be most liable to these unpleasant experiences.—I am, etc.,

R. N. HERRINGTON.

Southern General Hospital,
Glasgow S.W.1.

REFERENCE

[1] Shagass, C., and Jones, A. L., *Amer. J. Psychiat.*, 1958, **114**, 1002.

SIR,—Nearly ten years ago I wrote (*Brit. med. J.*, 1952, **1**, 330) suggesting that the use of a (then new) short-acting relaxant with anaesthetic cover could revolutionize the administration of, and hence the attitude of the patient towards, electroplexy. During trials suxamethonium iodide (or bromide) solution was mixed with the barbiturate, but it was found that the suffocation effect hit the patient before narcosis was achieved; the two-syringe method followed.

Since that time I have found it desirable always to check with my anaesthetist on the very point that Dr. W. E. R. Mons now humanely raises (July 29, p. 307). It is necessary to have the patient *deeply* asleep—not less than 0.35 g. of barbiturate will do—and there should not be any hurry to follow with the relaxant. It is better to have more than less of the latter—a little more can do no more harm (prolonged apnoea is rare—I have never met it in something like 2,000 patients), whereas too little could permit damage. Apart from ensuring that the prodromal effects are not suffered, the post-operative management is, in my view, most important. It is a mistake to aim at treating as many patients under anaesthetic and relaxant in the same time as it would take "straight." Patients should remain in a quiet, darkened room to sleep until waking spontaneously—the longer the better; they are less confused and therefore less liable to be disturbed by unfamiliar surroundings; a friend or relative should be sitting quietly by the bedside—instructed not to talk or

touch the patient when he first wakes, since he will fall asleep again and finally wake in a good state.

Management in hospital need be no less efficient and humane than in private practice—the clinic sister, her staff, and the anaesthetist must be concerned with the patient as well as with the treatment. In my out-patients' clinic the patient is moved as soon as respiration is restored but while he is still unrousable (trolleys will always knock against a door post or other object), to rest in a cubicle until waking; a cup of tea and so home with the escort. Apprehension does only very rarely become manifest; it is usually part of the illness and should not be a consequence of treatment.—I am, etc.,

London W.1. LOUIS ROSE.

Staphylococcal Infections

SIR,—In the leading article on controlling the hospital staphylococcus (August 5, p. 361) you conclude by emphasizing the need for smaller wards and more and better isolation rooms.

May I add to this the plea, to those planning new surgical departments, that pre-operative, cubicalized blocks should be brought into being? At present a patient comes into the surgical ward one or more days prior to his operation, and very soon his nasopharynx is colonized by the hospital staphylococcus. Having picked up the organism in his nose, he then scatters it over his immediate environment, as was shown by Professor Ronald Hare and Dr. E. M. Cooke (August 5, p. 333). On the morning of his operation he has a bath, but returns to his own bed immediately afterwards with the sheets and blankets teeming with staphylococci. Admittedly he puts on a theatre gown, but by the time he arrives at the theatre his whole environment as well as his nasopharynx is still laden with the organisms. Despite all measures to prevent air turbulence in the theatre these become airborne and some may settle in the depths of the wound. If on the other hand no pathogenic organisms have been enclosed in it, the wound is probably safe from organisms on its surface, once the skin closure has been completed. He can then return to the staphylococcal environment of the ward, and should come to no harm other than that of taking the ward staphylococcus home to his friends and family.

May I suggest that a surgical patient admitted from the waiting-list should come into hospital direct into a fully cubicalized ward, without communal "up rooms" or dining-rooms and other facilities to infect the nares of his fellow patients? He should remain in hospital for as short a time as possible before his operation. The nurses and orderlies may become carriers, but as they would be few it would probably be practical to take regular nasal swabs from them. Fraternization would be discouraged and patients kept as segregated as possible. Just prior to his operation the patient would bath, using a soap such as hexachlorophane, and would wash his hair. He would dry on a clean towel and put on his theatre gown. He would not go back to his own cubicle, but would have his pre-operative injection and would lie on a clean stretcher-top in a special pre-operative room so designed that stretcher poles could be put in easily and so avoid the lifting on to the chest by the porters so often practised in hospitals at present. Two or three rooms would be necessary in each pre-operative ward. On return from the theatre the patient would return to the infected atmosphere of the main ward, and of course emergency admissions would by-pass the pre-operative ward.

By this arrangement the patient would be delivered to the theatre with the least chance of bringing the ward staphylococcus with him, and, if his wound does subsequently become infected, there would be the least risk of his infecting another patient who was just about to go down to the theatre. If one believes that 95% of wound infection gains entry in the theatre, the ritual of much of the wound-dressing techniques becomes unnecessary. After all, one does not as a rule dress a wound until the stitches are due for removal; then it is either healed or infected. If it is healed it is impervious to bacteria, and if infected it is impossible to infect it further.

On the assumption that wounds are infected in the theatre let us try to deliver our patients there as surgically clean as possible, and this can only be achieved by admitting them to cubicalized pre-operative wards.—I am, etc.,

Norfolk and Norwich Hospital, Norwich. J. P. STEPHENS.

SIR,—Your leading article on the control of the hospital staphylococcus (August 5, p. 361) raises an important problem. I agree with all the proposed improvements—i.e., disinfection of bedding, baths and bath water, urine bottles, and crockery. The emphasis placed on the danger of multiple resistant strains of *Staphylococcus aureus* is timely and time-saving. Surgical units with smaller wards and more numerous and better-constructed isolation rooms are urgently required nearly everywhere. The great danger to other patients of a case with staphylococcal lesions of the skin, staphylococcal pneumonia, or staphylococcal enterocolitis, as indicated by Professor Hare and Dr. E. M. Cooke (August 5, p. 333), is evident. The umbilical wound should be treated,[1] and the newborn's nose.

A point which I should like to make (and which is not treated by any of the papers quoted above) is that nurses should wear sterile thin rubber gloves when handling babies and adult patients.[2] Wolinsky, Lipsitz, Mortimer, and Rammelkamp[3] have emphasized the danger of spread predominantly from the hands of the carrier to the infant.—I am, etc.,

Pathology Department, St. Margaret's Hospital, Epping, Essex. FRANK MARSH.

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1 *Lancet*, 1961, **2**, 192.
2 Marsh, F., ibid., 1958, **2**, 588.
3 Wolinsky, E., Lipsitz, P. J., Mortimer, E. A., and Rammelkamp, C. H., ibid., 1960, **2**, 620.

Phenindione and Blood-coagulation Factors

SIR,—Professor P. A. Owren's letter (June 10, p. 1679) and Dr. F. Nour-Eldin's letter (June 24, p. 1831) commenting on the paper by Mr. K. W. Denson (April 29, p. 1205) prompt me to join the discussion on the sensitivity of the thrombotest to Christmas-factor deficiencies. In our opinion Professor Owren made an incomplete quotation from the conclusions of Mr. Denson by mentioning only the Christmas assay of less than 1% corresponding with a value of 50–80% by the thrombotest method, linking this with the statement that thrombotest has been devised for the control of anticoagulant therapy and not as a test for disclosing Christmas disease. The relative insensitivity of the thrombotest to Christmas factor in two patients receiving anticoagulant therapy is, however, clearly demonstrated by Fig. 4 from the paper by Mr. Denson. Also the more modest aim of the thrombotest—to be sensitive to

Christmas-factor deficiencies at low levels of other coagulation factors—is not achieved.

Dr. F. Nour-Eldin repeats the theoretical objections he raised in 1959.[1] I would like to quote Professor Owren's answer to Dr. Nour-Eldin at the time in his letter in the *Lancet*.[2] "Whenever a theory contradicts a fact, the theory is likely to be wrong" . . . "The fact is that the thrombotest *is* sensitive to variations in the concentration of Christmas-factor activity (see Fig. 4 on p. 755 in my paper of Nov. 7)." When we consider this Fig. 4 in the *Lancet*,[3] or the identical Fig. 2 from Professor Owren's publication in *Farmacoterapi*,[4] it is clear that the sensitivity of the thrombotest to Christmas-factor deficiencies cannot be of any practical importance. For the coagulation times, measured with the thrombotest reagents, in the therapeutic range of 10–30% coagulation-activity range from ±50 to 100 sec.,[3] or in the therapeutic range of 10–25% coagulation-activity from ±70 to 120–160 sec.[4] From the quoted Fig. 4 in the Lancet and from the identical Fig. 2 in *Farmakoterapi* it appears that a concentration of 0% factor IX (at factor II, VII, and X concentrations of about 20%) produces a clotting time with thrombotest of 120 seconds. In other words a (nearly) complete disappearance of Christmas-factor produces a thrombotest result scarcely above, or in, the therapeutic range for anticoagulant therapy. The significance of the quoted figures is further reduced by omitting the correlation curve for the batch of thrombotest reagents Professor Owren used for this experiment and by the fact that the figure is composed of the results obtained with the plasma of only one patient.

I would like to suggest further proof before accepting Professor Owren's statement on the practical significance of the Christmas-factor sensitivity of thrombotest.—I am, etc.,

Department of Internal Medicine, St. Franciscus Hospital, Rotterdam, Netherlands. P. W. FREDERIKS.

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[1] Nour-Eldin, F., *Lancet*, 1959, **2**, 913.
[2] Owren, P. A., ibid., 1959, **2**, 1036.
[3] —— ibid., 1959, **2**, 754.
[4] —— *Farmacoterapi*, 1959, **15**, 92.

Methoserpidine in Hypertension

SIR,—The recently reported clinical trials of the use of methoserpidine ("decaserpyl") in the treatment of hypertension[1 2] prompt me to report my own experiences with this drug during the past two years. All the seven cases treated were previously stabilized on reserpine, and all complained of depression and drowsiness, which had previously been treated by the addition of methyl phenidate hydrochloride to the reserpine. The types of hypertension treated were: (1) One case of pre-eclamptic toxaemia of pregnancy, (2) two cases of arteriosclerotic hypertension, (3) one case of malignant hypertension, and (4) three cases of essential hypertension.

In all cases methoserpidine was found to control the blood-pressure equally as well as reserpine, and in no case was any side-effect (drowsiness or depression) noted. I believe that methoserpidine is probably the drug of choice in the treatment of moderate hypertension in patients for whom mental alertness is important.—I am, etc.,

London S.E.15. G. W. CARP.

REFERENCES
[1] General Practitioner Research Group, *Practitioner*, 1961, **186**, 768.
[2] Holt, M. C., *Brit. med. J.*, 1961, **2**, 415.

Renal Biopsy in Gout

SIR,—I read with great interest the article on renal biopsy in gout by Drs. D. Greenbaum, J. H. Ross, and V. L. Steinberg (May 27, p. 1502), work for which I send my best congratulations to the authors. However, contrary to what they say, this subject has already been investigated. For three years, with the help of my assistant, Mr. A. Gaucher, I have been studying the state of the kidney in gout, by means of percutaneous renal biopsy.[1–3]—I am, etc.,

Department of Rheumatology, University of Nancy, France. PIERRE LOUYOT.

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[2] Louyot, P., Rauber, G., Huriet, C., and Gaucher, A., *J. Urol. méd. chir.*, 1959, **65**, 628.
[3] Louyot, P., Gaucher, A., and Mathieu, J., ibid., 1961, **67**, 20.

Pathology of Anaemia

SIR,—I was particularly interested in the first of Professor L. J. Witts's Lumleian Lectures on this subject (August 5, p. 325). The concept of ineffective erythropoiesis occured to me after reading R. R. Bomford's paper[1] entitled "Haematological Heresy," and in a letter published in the *Journal* a few weeks later I suggested[2] that all the phenomena of pernicious anaemia, including bilirubinaemia, haemosiderosis, and increased excretion of urobilinogen, could be explained by the destruction of defective red-cell precursors, probably at the stage of extrusion of the nucleus, so that they never appeared in the blood-stream as reticulocytes. I even adapted the motor-car-factory analogy in much the same way as Professor Witts does towards the end of his first lecture and added that I hoped that tracer studies might one day prove or disprove the hypothesis. It is gratifying to learn that such methods do in fact lend considerable support to the theory, even if it cannot yet be regarded as finally proved.—I am, etc.,

Canadian Red Cross Memorial Hospital, Taplow. F. E. T. SCOTT.

REFERENCES
[1] Bomford, R. R., *Brit. med. J.*, 1946, **2**, 996.
[2] Scott, F. E. T., ibid., 1947, **1**, 112.

SIR,—I have read with very great pleasure Professor L. J. Witts's first Lumleian Lecture (August 5, p. 325), and was specially interested in his remarks on red-cell survival. Iron-deficiency anaemia interested me for many years, and I wrote an M.D. thesis on the subject in 1948. At that time, estimations of the duration of life of circulating red cells varied from about 30 days[1] to 120 days from Professor Witts's department.[2]

Solutions of saccharated oxide of iron for intravenous use were introduced then, and this made it possible to restore the body's iron requirements in a very short time. I usually gave 10 ml. on successive days, and on one occasion gave 10 ml. three times a day, which resulted in the complete treatment of a severe anaemia in 2½ days. In this particular case there was a significant reticulocytosis 40 hours after the first injection.

After this treatment, red-cell counts increased and reached peaks, frequently as high as six million per c.mm. about the 35th day, and thereafter slowly subsided to the accepted normal level of about five million. I only had simple apparatus and had to use the colour index as part of my information about progress. This frequently reached a

value of about 0.85 in 35–40 days, and thereafter very slowly reached unity in about double that time. So it was evident that, although nearly normal values were obtained for haemoglobin levels and red-cell counts in about 35 days, change continued for longer periods.

New red cells begin to appear in three or four days after the start of this treatment, and when the initial anaemia is severe (Hb 40% or less) there is no difficulty in differentiating the new red cells from the old on stained films—the new are large, circular, and well stained in contrast to the old ones, which are much smaller, poorly stained, and frequently misshapen. When serial blood films are examined it is seen that the old "anaemic" red cells only disappear from the peripheral blood in large numbers after the 35th day. This explains the high red-cell counts at this time and the continuing increase in colour-index values after this time. In three cases which were examined at weekly intervals, the red cells on stained films did not become completely normal until 100, 102, and 113 days respectively, and these terms must represent the longest life of "anaemic" red cells in the three cases studied.

One could easily do differential counts of these old and new red cells, and, with total red-cell counts done at the same time, produce an informative graph of the old cell population. I never did this, because at the time it was a distraction from my main objective for my thesis, and soon afterwards labelled cobalt and iron began to be used in the study of the life of red cells, and I thought I should be wasting my time. Professor Witts's last paragraph of his section on red-cell survival suggests that further use might be made of this very simple technique.—I am, etc.,

Kidsgrove, Staffs. DOUGLAS FRENCH.

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[1] Schiødt, E., *Acta med. scand.*, 1938, **95**, 49.
[2] Callender, S. T. E., and Nickel, J. F., *Proc. Central Soc. clin. Res.*, 1947, **20**, 6; also *J. Lab. clin. Med.*, 1947, **32**, 1397.

Betamethasone

SIR,—I read with some surprise a letter from Dr. R. O. Gillhespy (August 12, p. 454) on the use of betamethasone. After treating 36 cases of rheumatoid arthritis for unstated periods of time, he comes to the "opinion that betamethasone is not as efficient a corticosteroid as some already in common use." He thinks that "betamethasone showed a poor anti-inflammatory corticosteroid effect." Dr. Gillhespy does not say how he assesses this effect in rheumatoid arthritis. In the skin, however, inflammation is readily seen: in an experience of this drug spread over 14 months and more than 200 cases of skin disease I have found that inflammation readily and rapidly disappears with a proper dose of betamethasone.

It seems to me nonsense to expect corticosteroids of different structure to be assessed on a tablet-for-tablet basis: nor is it reasonable to expect manufacturers thus to market their products. After all we don't expect a tablet response with barbiturates or sulphonamides. There are, too, different strength tablets of some of the corticosteroids. The dose of each new corticosteroid can only be established according to the need of the individual patient and the rough average dose only after considerable clinical experience. I suspect that Dr. Gillhespy used too small a dose.

The incidence in this series of side-effects was higher than that seen by others. Can he, perhaps, have been led into the old trap of blaming all the patients' ills to the drug? Fortunately none of his patients suffered from anything but minor ills such as are common with all corticosteroids.

My experience with betamethasone has been a happy one. I find it usually as good as prednisone, sometimes better, no more likely to cause side-effects, and its price attractive.—I am, etc.,

London W.1. DAVID WILLIAMS.

SIR,—The letter by Dr. R. O. Gillhespy (August 12, p. 454) concerning his experience with betamethasone ("betnelan") suggests the advisability of further extended trials. With any therapeutic preparation this is always commendable and right, but his initial pilot trial appears at variance with others, and certainly with my own experience.

I have undertaken a very similar trial on a selected series of 23 rheumatoid arthritis cases (82% with positive Rose–Waaler), who were already stabilized on some other steroid and were at the time already suffering with "moon-face." Results showed that the clinical equivalence dose of prednisone/betamethasone was 7.9/1. Thus one 0.5 mg. tablet of betamethasone was approximately equal to 4 mg. prednisone. Assuming the accepted relative equivalents of other steroids, the mean stabilization dose before the trial was 8.3 mg./diem. Dr. Gillhespy's dosage of 2–6 tablets a day is therefore equivalent to 8–24 mg. prednisone a day. The higher level is one with which side-effects are to be expected.

In comparison with Dr. Gillhespy's figures (in brackets), my series showed two cases, 8.3%, who failed to respond satisfactorily (33%). Three cases, 13%, had to cease or alter the steroid because of side-effects (54%). Minor digestive troubles and giddiness occurred only in one case each. Other side-effects were less than with a number of other steroids, particularly in absence of digestive troubles, oedema, or general gain in weight.

Individual variation to systemic synthetic steroids is likely to be in the same range as the many reported variations to the intra-articular administrations. Variations in these initial pilot trials is comparable to similar variations during the initial investigations on phenylbutazone, which emphasized that with time and larger-scale trials a more stabilized picture will emanate. With my own experience to date and on the above equivalence data, betamethasone appears to be as satisfactory a corticosteroid as many others, and in a number of respects it has some advantages.—I am, etc.,

HARRY COKE.

London W.1.

Tennis Elbow

SIR,—I found your annotation on tennis elbow (August 12, p. 439) most interesting. I should like to mention a possible cause of the trouble in the relatively small proportion of cases occurring in tennis players. It is perhaps not well known that using too small a grip on the racket frequently causes tennis elbow. I personally have seen several instances where the trouble disappeared almost dramatically after the player changed his racket to one with a thicker handle.

The obvious conclusion from this is that squash and badminton players, using the smaller grips on their rackets, should invariably get tennis elbow. Presumably the different actions of the strokes in these games usually prevent it.—I am, etc.,

London W.C.1. COLIN MADDOX.

SIR,—I was surprised that in your annotation on "Tennis Elbow" (August 12, p. 439) you first state that so little is known about this condition, and then

suggest a puerile pathology. I was then pained at the suggestion that the injection of a locally acting steroid has revolutionized the treatment. Such a statement reads like the specious claims of the advertisements we receive daily; it extols the treatment but gives no rationale for its use (except possibly the old adage that anything cures while it is new).

I suggested some years ago[1] that the pathology of this condition is a tender spot in the extensor origin, resulting from over-use of those muscles in one position —namely, fixing the elbow in the semi-flexed position, and often in a repetitive movement. In addition, those muscles have seldom, if ever, been put through complete full range of movement. The importance of full range of movement is a subject which has been sadly neglected.

For treatment about 4 ml. of 2% local anaesthetic is injected into the tender spot in order that a powerful thumb can loosen it up, in all positions of flexion and extension. Then finally it is loosened on full stretch—namely, elbow extended, wrist pronated and flexed, which is the position of the hand hoping for an illicit tip. As pointed out earlier, this position of full stretch is only practised by a small section of the community, and in my experience they do not suffer from tennis elbow. The after-treatment is important. The loosening up and full stretch must be maintained by a physiotherapist. The results are extremely satisfactory, but failures will occur if the tender spot is not properly localized and injected, or if the after-treatment is not properly carried out. It is perhaps worth mentioning that a number of the cases thus relieved had previously had injections of steroid without benefit.—I am, etc.,

Tunbridge Wells. W. H. GERVIS.

REFERENCE

[1] Gervis, W. H., *Orthopaedics in General Practice: Is it Rheumatism, Doctor?*, 1958. Heinemann, London.

Apnoea, Hypertension, and Conjunctival Oedema

SIR,—In the case Mr. E. C. Wood and I described (July 22, p. 217) it is certainly possible, as Dr. Gordon H. Bush suggests (August 12, p. 455), that the signs might have been caused by carbon-dioxide retention. In the list of differential diagnoses the phrase " at this stage " is used by us. The patient had then been, as we thought, hyperventilated for nearly two hours through a circle absorber, using a fresh gas flow of 7 litres per minute, and the obvious measure of changing the soda lime in the absorber had been taken. This was at the time thought to make carbon-dioxide retention impossible. However, the clinical impression of hyperventilation may have been incorrect, although there was no evidence of mechanical impairment of ventilation in this patient, and the soda lime may still have been defective. It does, however, seem unlikely that gross carbon-dioxide retention could occur under these conditions in so short a time (20 minutes). It is of course regrettable that no means of measuring blood or alveolar carbon dioxide, minute volume, or the state of neuromuscular transmission was available in this case, but this is still the rule rather than the exception when such problems arise clinically.

In spite of the excellent body of information now available on the management of prolonged apnoea, the best course for an anaesthetist confronted with this condition and with no ventilator, spirometer, nerve stimulator, or gas analyser to hand is still far from clear. While making no claim that the management of this case was ideal, I think that most anaesthetists would in such a situation prefer the intelligent use of drugs to complete inactivity.—I am, etc.,

Mount Vernon Hospital, Northwood, Middlesex. T. A. BOLISTON.

Cooling of Operating Theatres

SIR,—I can confirm the efficacy of the simple method of cooling, by using a fan to play on a large block of ice, described by Mr. Kenneth H. Pridie (August 12, p. 452). In the second half of July, 1938, when ship's surgeon in T.S.S. *Tuscania*, then on a cruise in the Mediterranean, I kept a small 8-bed female ward comfortably cool for an elderly passenger with cardiac asthma and on oxygen, for three days, from Monte Carlo to Tangier and past Gibraltar, by using electric fans to play, at medium speed by day and slow by night, on a ¼-cwt. block of ice lying in each of two butcher's skips.

Turbulence of this kind may be undesirable in operating theatres, but in the circumstances one has to balance risks, and, if the fans increase turbulence, the surgeons by perspiring less will shed fewer bacteria to be disseminated.—I am, etc.,

Chapel Brampton, Northants. J. F. HEGGIE.

Coloboma with Multiple Congenital Anomalies

SIR,—Four cases, all showing apparently distinct though related syndromes, have recently been seen, or referred, as cases likely to be the result of chromosomal imbalance, and it is perhaps worth reporting these as an addition to the interesting cases collected together by Dr. Harry Angelman (April 29, p. 1212), and to those reported by Drs. D. G. Cottom and Myrtle V. Richards in subsequent letters (May 27, p. 1540). Including our four cases these make 11. No two seem particularly similar. In none was any familial or parental manifestation evident. The non-familial nature of these cases is to some extent to be expected in that most conspicuous familial conditions, as frequent as this complex of signs appears to be, would probably be recognized by now as a distinct entity.

(1) S. N. (Hillingdon Hospital), a boy, the first child of young parents, was admitted because of neonatal feeding difficulties. Birth weight 6½ lb. (2.95 kg.). The baby made poor attempts at sucking, and feeding was often accompanied by cyanosis. On examination there was marked micrognathia. The ears were normal but low-set, and the neck, as seen from behind, appeared normal. Radiological signs of cardiac enlargement and pulmonary plethora were later consistent with a ventricular septal defect. The pupils were round, regular, and unequal in size, the right pupil being smaller than the left. Eye examination (Mr. I. Spiro) under anaesthesia showed a normal left retina. On the right side, a large coloboma of the choroid was present inferiorly, extending to the ora serrata. The coloboma was about three disks diameter in extent, and much pigment was irregularly arranged in the defect. Development has been severely impaired, and when last seen at the age of 3½ years he weighed 19½ lb. (8.85 kg.) and could not walk unaided. Chromosomal preparations from a fibroblast culture established from a minimal skin biopsy showed no abnormality.

(2) A. S., a girl, born after a 43-week pregnancy, weight 6½ lb. (2.95 kg.), had bilateral colobomata of both iris and choroid, microcephaly, micrognathia, talipes, severe mental retardation, and a cardiac murmur which later disappeared. An *x*-ray survey showed no further abnormality. The child had two normal sibs; one sib had died following a birth injury; her mother had miscarried twice at the third month.

Chromosomal studies carried out on a fibroblast culture established from a minimal skin biopsy, referred by post from the Department of Child Health at Newcastle, showed no abnormality.

(3) B. W. (Children's Hospital of Philadelphia, 61/37), a boy of Polish ancestry, the second child of a 20-year-old mother. The other child was normal. Birth weight 6½ lb. (2.95 kg.). A peculiar face with a small mandible and low-set anteriorly rotated ears, distorted by a right facial paralysis, was noted immediately. The lobes of the ears, particularly the right, were poorly formed. Ophthalmoscopy revealed deep excavations of the disk with bilateral posterior staphylomata. The palate was high. A pilonidal dimple was present. E.E.G. showed evidence of a diffuse and severe defect. Development was very slow and terminated by death at three months. Post-mortem examination confirmed the clinical and radiological diagnosis of patent ductus arteriosus, a right-sided aorta, and complete agenesis of the right kidney and ureter. The left kidney was normal and no other abnormality was found. Permission to examine the brain was refused. Chromosome preparations from lymphocyte culture showed no deviation from a normal male set of chromosomes.

(4) E. S. (Children's Hospital of Philadelphia, 61/23), a girl, the fourth child of a 31-year-old mother, the other children being normal, was admitted at the age of 4 days with convulsions accompanied by apnoea and cyanosis. On examination the facies was suggestive of mongolism although the eyes and their surroundings showed none of the usual signs apart from minimal epicanthic folds. The palate was normal, the mandible was small, the ears low-lying and anteriorly rotated, and the neck short with marked webbing. The eyeballs were small, and bilateral complete colobomata with inferior nasal clefts were present. The chest was shield-shaped and the nipples unusually small. The hands were stubby with short little fingers and a normal pattern of palmar lines. A large gap was present between the first and second toes. The anus was unusually anterior. Radiological studies of the head, chest, pelvis, and hands showed no abnormality apart from an unusual appearance of the tip of the sacrum. Buccal and vaginal smears showed infrequent Barr bodies of normal shape and size. A white-cell concentrate showed a normal proportion of typical drumsticks. The child died suddenly aged 3 months. A coroner's post-mortem examination defined the cause as thymic enlargement. Chromosomal studies of the child based on lymphocyte culture showed no definite consistent abnormality on complete analysis of 10 cells and partial analysis of 40 others. In view of the likelihood of this condition being due to a chromosomal aberration, and our difficulties in satisfactorily pairing the X chromosomes, both parents were then examined but no chromosomal abnormality was found.

—We are, etc.,

The Children's Hospital of Philadelphia, Pennsylvania, U.S.A. J. H. EDWARDS. R. B. YOUNG.
Hillingdon Hospital, Uxbridge, Middlesex. H. V. L. FINLAY.

Fusion of Labia Minora

SIR,—May I add two more to the cases already described (July 29, p. 314; August 12, p. 454; August 19, p. 523)? Each had an orifice admitting only a probe, and in both the underlying anatomy was essentially normal. One was a married woman of 69 who stated that her symptoms had developed gradually from the time of a "repair" operation ten years before.

The other, aged 56, was unmarried; she had no urinary infection. She made it clear after operation that hitherto, within memory, she had never had a normal act of micturition, although her really troublesome symptoms had only developed three years before. There was nothing in her history to suggest a possible cause until she remembered what must have been a severe attack of acute vulvovaginitis when she was about 4 years old.—I am, etc.,

Glasgow C.3. HELEN F. WINGATE.

Paediatrics and Psychiatry

SIR,—The reference (July 15, p. 168) to the paediatrics "combined clinics," in which the paediatrician and the psychiatrist or psychiatric social worker participate, will undoubtedly attract the attention of various workers in these fields. The statement, moreover, to the effect that this type of pioneering experiment should be widely encouraged prompts me to advise you that there is available information which should be useful to those who intend to explore this integrated approach to the mental, emotional, and social aspects of the paediatric patient.

Such clinics, known here as "integration conferences," have been conducted locally for almost a decade now, with very worth-while results. A good deal of credit is due to Dr. Walter Buerger, paediatrician, former staff member of Memorial Hospital of Long Beach, California, who provided the leadership in setting up these conferences in our hospital, as well as in the local county hospital for indigents. A very detailed description of how these conferences are organized and conducted has been published.[1]—I am, etc.,

Department of Medical Education, Memorial Hospital of Long Beach, Long Beach, California. GEORGE X. TRIMBLE.

REFERENCE

[1] Buerger, W. R., Wright, P., and Beam, E., *Calif. Med.*, 1960, 92, 403.

Management of Refractory Obesity

SIR,—I was interested to read Dr. A. E. Stevens's letter (July 29, p. 312) on management of refractory obesity. For cases of "simple" obesity I have found two months of treatment too short a time to assess final results. Although patients may lose weight in the first two months of treatment with drugs, a further steady loss is rarely maintained.

"Put not your faith in drugs" certainly applies to the treatment of obesity in the present state of medical knowledge, and this has been my clinical experience.[1] Briefly, the whole treatment of obesity depends on the skill of the doctor in being able to persuade the patient to eat less. Drugs are of minor importance.—I am, etc.,

London W.1. JACK LIEBER.

REFERENCE

[1] Lieber, J., *Trans. Hunter. Soc.*, 1948-49, 7, 113.

POINTS FROM LETTERS

Nitrous Oxide in Dentistry

Dr. DONALD BLATCHLEY (London W.4) writes: May I, through you, thank Dr. Michael P. Coplans (July 22, p. 246) for the interest he has taken in my remarks? With respect, I suggest to him that, should his babies' rage proceed from local venous engorgement of the face to generalized anoxia from breath-holding, he should cease to regard it with complacency but take steps to stimulate respiration by administering a gentle smack on that part of the anatomy traditionally reserved for it.

Obituary

Sir HENRY BASHFORD, M.D., F.R.C.P.

Sir Henry Bashford, who was for thirty-six years a medical officer on the headquarters staff of the General Post Office, and for the last ten years of that period chief medical officer, died on August 15 at the age of 81. Whether the writing of books was a foil to his official work at St. Martin's-le-Grand, or his official work a foil to his literary labours, he found time to write, at first under the pseudonym of Peter Harding, many volumes of essays and stories which gave him a well-recognized place in literature and revealed him as a penetrating but kindly student of human nature.

[*Walter Stoneman*

Henry Howarth Bashford was born on January 13, 1880, the son of Frederick Bashford, of Northaw, Hertfordshire, and the grandson of the Rev. Henry Howarth, rector of St. George's, Hanover Square, and chaplain in ordinary to Queen Victoria. He was educated at Bedford Modern School and at London University, and took his medical training at the London Hospital, where he played for the first rugby fifteen and also for the United Hospitals. At the London he must have got material for many of his books: he could always afterwards recall "that faint but unmistakable smell of burnt coffee and human unwashedness which broods over Whitechapel Road." He qualified in 1904 and served in various house appointments at the London. Graduating M.B., B.S. in 1906, he proceeded to the M.D. two years later. In 1939 he became a Fellow of the Royal College of Physicians of London, having been elected a Member in 1934.

In 1907 Bashford became an assistant medical officer in the Medical Branch of the General Post Office, and in 1933 he was appointed Chief Medical Officer, being knighted in 1938. The medical service of the Post Office, dating back to 1855, is one of the oldest examples of an industrial medical service in Britain, and under Bashford it became one of the largest in the world. Its records provide a mine of information for research workers, and one of the interesting contributions Bashford himself made was a study of the improvement in the physique of young people in the 25 years before the second world war. London boys of 16 coming into the service of the Post Office were 16 lb. heavier and 1½ in. taller than their predecessors of 25 years before.

In 1943 Sir Henry Bashford left the Post Office and became Treasury Medical Adviser and responsible for a new medical service designed to cover the whole Civil Service. He resigned from this post at the end of the war. During his career he came to be recognized as one of the leading authorities on occupational health services, and he was a member of the Industrial Health Research Board. An obvious choice for the editorship of the *British Journal of Industrial Medicine*, the first number of which appeared in January, 1944, under the auspices of the British Medical Association and the Association of Industrial Medical Officers, he worked on the new journal for nearly a year before seeing the first issue to press, but his Treasury appointment obliged him to vacate the editorial chair.

A Knight of the Order of St. John of Jerusalem, he was always interested in the work of the St. John Ambulance Association, being president of the Post Office Ambulance Centre. From 1941 to 1944 he was an Honorary Physician to King George VI.

Like Anthony Trollope, Bashford's official work permitted him leisure for literary activity. The first of his books was partly written when he was still a student—a romance called *The Manitobans*, published in 1908. Much of his literary work, naturally, was coloured by his medical experiences. This is specially true of a delightful volume of letters to imaginary correspondents, written in the vein of traditional English essayists, entitled *The Corner of Harley Street*, published in 1911. Much good counsel concerning entrance on a medical career and on the handling of patients will be found in that small volume. It was succeeded by *The Harley Street Calendar*, and other well-known titles were *Pity the Poor Blind*, *Wiltshire Harvest* (he lived in Wiltshire, near Marlborough, after his retirement), *Behind the Fog*, a tale of adventure, *Half-past Bedtime*, *The Happy Ghost*, *Songs out of School*, and *Lodgings for Twelve*. With Archibald Hurd he wrote *Sons of Admiralty*. He also edited a volume called *Doctors in Shirt-Sleeves*, in which he induced some twenty prominent members of the medical profession to write amusingly on their hobbies, from the study of philosophy to trivial pastimes. He wrote a long introduction, almost a full-dress biography of Osler, to Osler's *Student Life and Other Essays*. He recognized in Osler, as many men of like temperament and gifts have done, a master.

In 1908 he married Margaret Eveline, daughter of Ernest Sutton, of Basildon, Berkshire, and had one son and three daughters. Lady Bashford died in 1955.

Sir ARTHUR MACNALTY writes: There have been many writers and novelists whose literary success has led them to relinquish their original calling. Others again, like Anthony Trollope, the Rev. S. Baring-Gould, Canon Hannay ("George A. Birmingham"), and Sir Andrew Balfour, have played a dual role in life and have followed the example of Sir Walter Scott, who wrote: "I determined that literature should be my staff but not my crutch." Henry Bashford was of this gifted and energetic company.

When *The Corner of Harley Street* was published in 1911, many speculations were advanced as to its authorship. So mature appeared the book's judgment and medical experience, so deep its philosophy, knowledge of life, and sympathetic outlook on the sorrows and joys of mankind, that it was regarded as the work of a much older man, the consensus of opinion attributing it either to Sir Frederick Treves or to Stephen Paget. Yet Bashford was only 30 years old when he wrote it. There is much of himself in the book, his love of angling, of general literature, and his kindly wit and humour. It is one of the best books of the century; and, although his other novels, biographical studies, and short stories have their charm and literary grace, this was his masterpiece.

My friendship with Bashford dates from the year 1912, when I was medical registrar at the London Hospital. I occasionally saw employees of the Post Office whom he had referred for an opinion or special treatment. His notes on these patients were always informative and precise, and he never omitted to acknowledge in courteous terms the advice he received. In later years Sir Kingsley Wood, as Postmaster-General, formed a high opinion of the chief medical officer's work, and when he became Minister of Health asked me to sound Bashford as to whether he would like to join the medical staff of the Ministry. Bashford preferred to remain at the Post Office to continue his important work on industrial medicine.

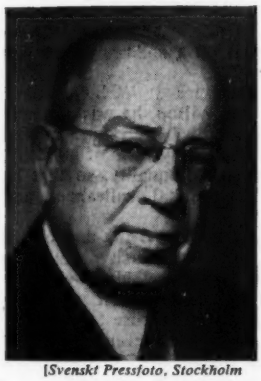
Looking through several of Bashford's letters to me, I found one written in 1939 saying: "I hope you are surviving all the storms and tempests of these troubled times," for he felt the waste and destructiveness of the war acutely. When he retired to Wiltshire I saw him less frequently, but we met at the College of Physicians from time to time. He took a large and generous part in launching the project of a fourth volume of Munk's *Roll*, an inestimable service to medical biography.

Henry Bashford said of the alabaster box of life when its breaking has seemed to be the end of all things: "Well, we can at least say this—that its perfume is still upon the air, its real gift to us and our great and permanent possession." That reflection will be of solace to his many friends to-day.

GUSTAV NYLIN, M.D., F.R.C.P.

Professor Nylin, formerly senior physician at Södersjukhuset, Stockholm, and a cardiologist of international renown, died on August 6 at the age of 68.

Karl Gustav Vilhelm Nylin was born in December, 1892, and graduated in medicine at the Stockholm Medical School. For several years he worked as a school medical officer, and during this time he collected for his M.D. thesis a mass of data about the growth of children. Deciding to devote the rest of his career to research work, he became an assistant at the Seraphim Hospital, Stockholm, and from 1933 to 1936 was head of the physiological laboratory there. This has influenced all his subsequent work, which has all been based on sound physiological principles. Then followed a period as lecturer at the Caroline Institute.



[*Svenskt Pressfoto, Stockholm*

During the war years he was chief physician at the Sabbatsberg Hospital, where he continued his investigation of cardiovascular disease. Here, in 1945, with his colleague Crafoord, he published the work for which he is perhaps most widely known, resection of the narrowed segment for coarctation of the aorta (*J. thorac. Surg.*, 1945, **14**, 347)—an operation that has proved of the greatest value and one that is carried out all over the world.

Nylin had already worked on the volume of the heart and had emphasized the importance of the residual blood in the failing heart. In 1945 he published some of the earliest work on the blood volume, using radioactive phosphorus (*Brit. Heart J.*, 1945, **7**, 81): he found an average value of 73.5 ml. per kg. of body weight in normal subjects and only a little less in patients with compensated heart disease. Since then, the use of radioactive substances, especially thorium, in the study of the volume of blood in the body as a whole, in the lung, and in the heart, and of the amount circulating to different parts, especially the brain, has been one of his main interests. In 1946 he joined the staff of the newly built Södersjukhuset, having taken part in the planning of its famous cardiological clinic.

In September, 1952, as president of the European Society of Cardiology, he played a prominent part in the First Congress, held in London under the chairmanship of Sir John Parkinson. He gave a charming address on the large part that had been played by British physicians and physiologists in the development of cardiology. He was elected an honorary member of the British Cardiac Society about this time. The last number of *Cardiologia* in 1952 was a *Festschrift* dedicated to Professor Gustav Nylin in honour of his sixtieth birthday and written by his friends and pupils. In 1955 he was elected F.R.C.P.

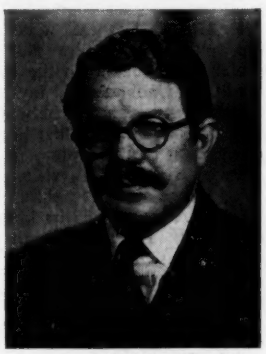
In September, 1956, the Second European Congress of Cardiology was held under his presidency in Stockholm, and the success of this meeting owed a great deal to the work he had put into it. At the end of it he was appointed one of the honorary presidents of the European Society, joining Professor Charles Laubry and Sir John Parkinson, for these three were the main founders of the Society.

In June, 1957, he was again in London for the Harvey Tercentenary Congress. With S. Hedland he read a comprehensive paper that summarized much of his work on the blood flow and pool in the heart, lungs, and brain. The writer has a vivid memory of talking to him and his charming wife, looking up at Canterbury Cathedral after the special service that had been held there for the Congress, and of hearing his appreciation of the many beautiful scenes that had given him so much pleasure in England. As a result of the large amount of work that he had carried out on the circulation, he was appointed in 1958 chief of scientific research in the isotope laboratory at Söderjukhuset. Gustav Nylin will be widely missed not only as a great scientific worker but as a central figure at many international meetings.—M. C.

Sir WALTER FERGUSSON HANNAY, M.R.C.S. L.R.C.P.

Sir Walter Fergusson Hannay, who practised in the West End of London, died on August 14 in the St. John and Elizabeth Hospital after a long illness. He was 56.

Walter Fergusson Hannay was born in London on November 22, 1904, and educated at Berkhamstead School and Guy's Hospital, where he won the Pembry prize of the Physical Society. Qualifying in 1928, he became resident medical officer at Horton General Hospital, Banbury, and thereafter, both before and after his entry into general practice, he held a number of clinical assistantships at London hospitals, including the Princess Beatrice Hospital, the National Heart Hospital, the West End Hospital for Neurology and Neurosurgery, and St. Mary's Hospital, where he was a senior hospital medical officer in the dermatological department. He was president of the Chelsea Clinical Society a few years ago.



[*Elliott and Fry, Ltd.*

Sir Walter Fergusson Hannay, who was knighted in 1951, had a large practice, and he was personal physician to Mr. (now Earl) Attlee during the latter's premiership. A vigorous opponent of the control of doctors by the State, he was a frequent contributor of letters to the national newspapers. Among subjects on which he held strong views were the harmfulness of diesel fumes and of excessive noise, and he was a past-chairman of the Noise Abatement Society and vice-chairman of the National Pure Water Association.

Until recently he had a country home in Hertfordshire and was president of the East Hertfordshire Liberal Association. He leaves a widow, Doris Leslie, the well-known novelist and writer of historical biographies.

Dr. DESMOND MACMANUS writes: It made me very sad to read of the death of my old friend, Sir Walter Fergusson Hannay. Others will have written about his brilliant professional career and clinical acumen. I like to remember the man—so popular and happy. He was socially charming, with a real appreciation of good food and wine, a delightful conversationalist, and a witty after-dinner speaker. We had a mutual bond in that we were both inveterate snuff-takers. He will be greatly missed by a host of friends and patients—with him the terms are synonymous—and especially at the Chelsea Clinical Society, of which he was an excellent president and at the Round Table, to which he was chirurgeon.

H. T. BARRON, M.D., M.R.C.P.

Dr. H. T. Barron, consulting physician in diseases of the skin to the Westminster Hospital and Croydon General Hospital, died on August 12. He was 85.

Henry Thompson Barron was born in Portsmouth in 1875, the son of the Rev. Henry Barron. Educated at the City of London School, he studied medicine at the Westminster Hospital, to which he won an entrance scholarship. He graduated M.B. in 1898, and after holding the post of house-physician at the Westminster he became medical registrar there from 1900 to 1902. He then went into practice in Balham, being medical officer to the Balham Dispensary. He was always interested in dermatology, and, having gained valuable experience as chief assistant in the skin department of St. Thomas's Hospital, he secured the honorary appointments of dermatologist to the Royal Waterloo Hospital and Croydon General Hospital, and assistant physician to the skin department at the Westminster Hospital. In addition he had a consulting practice in Queen Anne Street. Evenually he became physician to the skin department at the Westminster Hospital, medical officer to the V.D. clinic there, and lecturer on diseases of the skin in the medical school as well as at the London School of Dermatology. He was elected M.R.C.P. in 1927.

Dr. Barron was a former secretary and vice-president of the Section of Dermatology of the Royal Society of Medicine, and an elected member of the British Association of Dermatology. Among the contributions he made to the literature of his specialty was an article on ichthyosis in the *British Encyclopaedia of Medical Practice.*

Dr. P. M. DEVILLE writes: Dr. Barron was a modest, unassuming man who did not seek the limelight and preferred to remain in the background. He had all those qualities of honesty and loyalty that distinguish the upright English gentleman that he was.

He was one of the first practitioners to own a motor-car at the turn of the century, giving up the carriage and pair with which he did his visits at this time, and he continued to be a keen motorist right up to his last illness. He obtained the bronze medal for the London to Edinburgh car rally in the 1920s. He was also an expert gardener, and nothing would please him more than to show his friends over his garden, to which he devoted a great deal of his leisure at his Streatham Park home. It was not generally known that he was an accomplished conjurer and that he was an elected member of the Inner Circle of the Magic Circle, a distinction accorded only to those magicians of proved ability.

Dr. Barron married later in life and his wife predeceased him about two years ago. There are no children. He will be sadly missed by his circle of friends and by his colleagues.

T. E. LENNON, M.D., F.R.C.O.G.

Mr. T. E. Lennon, whose untimely death at the age of 53 took place on July 19 after a long struggle against an intractable disease, was consultant gynaecologist and obstetrician to the Birkenhead and North Wirral group of hospitals and consultant gynaecologist to the Providence Hospital, St. Helens.

Thomas Emmett Lennon, who was born in south-west Lancashire on April 22, 1908, belonged to a family well known in the St. Helens area. Educated at the Catholic Grammar School, St. Helens, and Liverpool University, where he held the Robert Gee fellowship in anatomy, he graduated M.B., Ch.B. in 1931 and proceeded M.D. five years later. After graduation he held the posts of senior resident obstetric officer at Walton Hospital and resident obstetrician, registrar, and tutor in obstetrics at Liverpool Royal Infirmary. He took the M.R.C.O.G. in 1938 and was elected F.R.C.O.G. this year.

S. B. H. writes: After holding preliminary resident posts at the Liverpool Royal Infirmary, "Tommy" Lennon, as he was known to a host of friends and colleagues, entered upon an association with Walton Hospital for some thirteen years. In that very large gynaecological and obstetrical unit he gained the wide practical experience which was to render his subsequent work as consultant so valuable and enabled him to build up the successful practice that he later enjoyed and win the professional confidence of so very many medical and nursing colleagues as well as that of a great number of patients of all walks of life who gained so greatly from his skill and kindness. When, after the war, he joined the staffs of the Birkenhead and North Wirral Hospitals his typical Lancashire integrity and quietly confident yet skilful handling of patients established a tradition that will long be remembered.

One may be permitted a personal tribute to a close colleague and friend with whom it was possible to have a well-nigh perfect association for the past twelve years. In these years (until the recent advent of a third member of the team), during which we divided the responsibility for emergency calls and all clinical sessions in five hospitals, he never once failed to be available when called upon and was punctilious in attendance at all hospital occasions, so that one came to lean on him as on a colleague who was quite infallible.

In spite of the extensive experience at Walton, gained under the aegis of Mr. St. George Wilson, he was as ready to take as to give advice, and, although by nature modest and possessed of a natural aversion to any form of publicity, he bore in his work the hall-mark of quality, so that he was trusted and consulted by hospital colleagues and practitioners alike.

In his earlier years he was interested in flying and played Rugby football, being capped for his university. Later he became a keen golfer. Many who knew him well were aware of the brave fight he made against what proved to be a fatal disease, but he made this no excuse for relaxing in his devotion to work, and, in fact, he even insisted on carrying out full duties for a while after commencing a drastic and somewhat distressing course of treatment.

The respect and admiration felt by many were proved by the presence of an overflowing congregation at his memorial service and by the wave of sympathy that has gone forth to his courageous wife (who, as Grace Dawson, was herself a gynaecologist and obstetrician) and his young family, from whose love he drew such great solace and in whose companionship he found his greatest happiness.

J. PRESTON MAXWELL, M.D., F.R.C.S., F.R.C.O.G.

The obituary of Professor J. Preston Maxwell was published in the *Journal* of August 12 (p. 457).

Professor W. C. W. NIXON writes: It comes to few to influence medical thought and practice throughout the length and breadth of a continent, but such was Preston Maxwell's achievement. He was appointed professor of obstetrics in 1919 at Peking Union Medical College, which had been built through the munificence of the Rockefeller Foundation. It was here that he exercised such a wide influence on contemporary and future obstetric practice in China. The P.U.M.C. became the Mayo Clinic of Asia, and during the 18 years there he built up a department that became a Mecca to which we made pilgrimage from afar. Generations of students and nurses passed through his hands who later introduced Western medical science to the provinces far distant from Peking. Some were destined to become leaders and teachers in the emerging modern hospitals.

Although administration and teaching, in which he excelled, took much of his time, yet he did not neglect research. His outstanding contribution was to the subject of osteomalacia, and this classical and monumental work gained in U.S.A. for this disease the eponym "Maxwell's disease."

To me and other tyros coming to the Orient, Preston Maxwell's presence in Peking was comfort and support. Always ready with advice and prepared to answer any call—he travelled a thousand miles to aid me over difficulties in my early days in Hong Kong—he helped us to orientate

ourselves and learn from a civilization that had stretched continuously for five thousand years.

His was a life of dedication to China, and no one could have better epitomized the dictum of Confucius that "within the four seas all men are brothers."

R. M. GORDON, O.B.E., M.D., Sc.D., F.R.C.P. D.P.H., D.T.M.

The obituary of Professor R. M. Gordon was published in the *Journal* of August 5 (p. 387).

Professor W. E. KERSHAW writes from Rangoon: Professor R. M. Gordon's scientific achievements are known to all in tropical medicine and parasitology, and many know of his contributions to the promotion and organization of research, but few were privileged to share with him his great wisdom, his high ideals, and his sense of purpose. His generosity of mind, kindliness, and geniality were proverbial and were manifested in a formality which was regarded as an endearing trait. These obvious characteristics were part of a deep wisdom which, while warm-hearted, had been tempered by a rigorous discipline of experience and a profound intellectual sincerity.

Some of his views were declared before they could be accepted, as are the views of all pioneers. To wonder whether urinary schistosomiasis was as pathogenic as was commonly believed was dismissed by many as pedantry; only now is a serious attempt being made to define the effects of this infection.

His insistence over many years that control measures must be based on accurate knowledge derived from research, and that such measures must be capable of modification by constant research, was misinterpreted by many as a reluctance to engage in control. Such were his sense of justice and his charity that he felt no animosity towards those who in honesty did not share his views, but he was exasperated that such lack of percipience—as it seemed to him—might in the long run cause precious time to be lost in bringing infections under ultimate control.

His own honesty made him vulnerable to intellectual dishonesty, speciousness, and anything unworthy, both on their own account and because they might debase the intellectual currency; and the disappointment and pain he felt on encountering them was hurtful for his friends to witness. He was ever generous, but knew that he must be just. His sense of duty and his selflessness made him unaware of how much he meant and means to others.

Mr. C. W. FRANCIS

The obituary of Mr. C. W. Francis was published in the *Journal* of August 5 (p. 390).

Dr. O. C. CARTER writes: I was shocked to read of the death of Mr. C. W. Francis. Your obituary gave a worthy account of the work which he did for the Association's publications, and I would like to add my tribute to an official of the Association whom I had known intimately over a period of twelve years, during which I was chairman of the Journal Committee. I held in highest regard his business acumen, complete integrity, and unfailing loyalty to the Association.

Mr. Francis was in charge of a large and very busy department over the past 24 years, and during that time there were two crises connected with publishing—first, during the period of the war, and, secondly, about ten years ago when the price of paper climbed to astronomical heights and caused a number of publications to fold up and cease publication. But Mr. Francis always thrived on difficulty and adversity, and he leaves behind a department so well staffed and organized that in itself it is a tribute to his outstanding ability and the value to the Association of the 24 years during which he held such an important position in *Journal* affairs. I would like to add my expression of sympathy to the widow and family whom Mr. Francis has left behind.

Universities and Colleges

UNIVERSITY OF CAMBRIDGE

Dr. John Michael Walshe has been elected to the E. G. Fearnsides Scholarship for 1961.

In Congregation on August 5 the following degrees were conferred:

M.D.—*A. P. C. Bacon, *E. W. Price, *A. J. H. Tomlinson, *W. McC. Edgar, *C. B. Mortimer, *S. Shaldon, L. G. Whitby, E. B. Verney.

M.B., B.CHIR.—*W. J. Norman, *D. J. Evans, Frances R. Jordan, *N. Jankey.

M.B.—*M. T. S. Roberts, I. Phillips, R. H. Elready-Cole, *R. D. Pyrah, M. J. Denham, *Sarah E. Bundey, *Gwendolen D. Loft, *Marian N. Sampson, Jennifer M. Charlton, Suan Yew Lee.

Professor E. B. Verney, F.R.S., has been elected into an Honorary Fellowship of Downing College from October 1, 1961.

*By proxy.

UNIVERSITY OF BIRMINGHAM

In Congregation on July 15 the honorary degree of LL.D. was conferred on Professor James M. Mackintosh, professor of public health at the London School of Hygiene and Tropical Medicine from 1944 to 1956, and now consultant adviser and director of medical education and training for the World Health Organization.

On July 15 the degree of M.B. was conferred on John Richard Moore, the degree of Ch.B. having been conferred *in absentia* by special warrant on June 19, 1961. Through an oversight Dr. Moore's name did not appear in the list of successful candidates in the *Journal* of July 29 (p. 318).

ROYAL COLLEGE OF SURGEONS IN IRELAND

On July 20 the Fellowship in Surgery of the College was conferred on A. N. Henry.

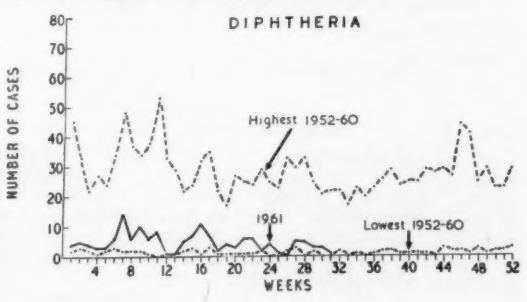
Vital Statistics

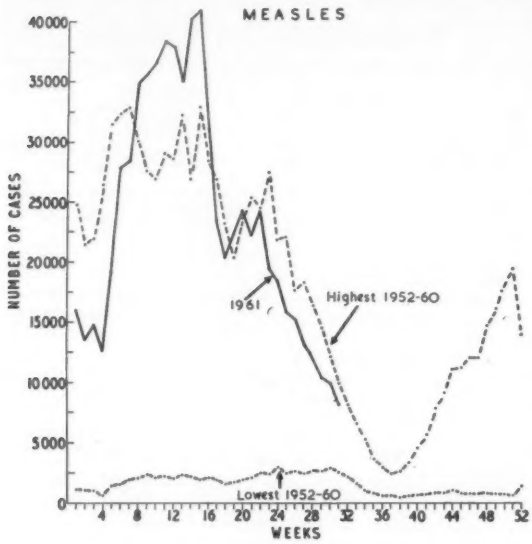
Cholera in Hong Kong

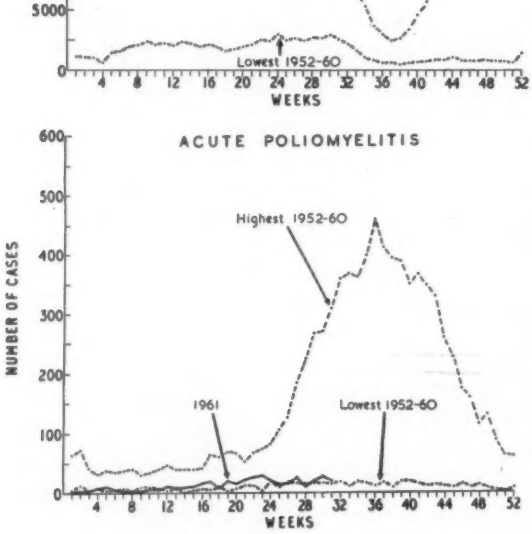
The appearance of cholera in Hong Kong and Macao lends substance to recent reports that there have been cases of cholera in southern China. Up to August 21 32 cases of cholera had been confirmed in Hong Kong, with 3 deaths. In addition there were a number of suspect cases, and 173 contacts had been isolated. A mass vaccination campaign has been put in hand, and about one million of the 3,200,000 population had been vaccinated by the end of last week. Increased supplies of locally prepared vaccine will be available this week, and in the meantime vaccine has been flown in from India, Britain, Sarawak, Australia, and the United States. According to press reports about 100,000 persons were inoculated on August 17, and 250,000 on August 21.

Graphs of Infectious Diseases

The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figures reported in each week during the years 1952–60 are shown thus ------, the figures for 1961 thus ———. Except for the curves showing notifications in 1961, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.







Infectious Diseases

Areas where the numbers of notifications were high in the latest two weeks for which figures are available

	Week Ending Aug. 5	Week Ending Aug. 12
Dysentery		
Hampshire	7	**12**
Gosport M.B.	6	**11**
London	33	**78**
St. Pancras	1	**24**
Southwark	19	**28**
Enteric Fever		
Middlesex	1	**5**
Willesden M.B.	1	**5**
Diphtheria		
Warwickshire	1	**2**
Birmingham	1	**2**

Death from Vaccinia

A 27-year-old-miner, of Forest Town, Mansfield Woodhouse, died on August 4 as a result of contracting vaccinia from his recently vaccinated 4-year-old and 16-month-old daughters. This very rare fatal mishap was thought to have been due to the transmission of the virus on a towel to the father, who had chronic eczema on the face, neck, and behind the ears.

INFECTIOUS DISEASES AND VITAL STATISTICS

Summary for British Isles for week ending **August 5** (No. 31) and corresponding week 1960.

Figures of *cases* are for the countries shown and London administrative county. Figures of *deaths* and *births* are for the whole of England and Wales (London included), London administrative county, the 17 principal towns in Scotland, the 10 principal towns in Northern Ireland, and the 14 principal towns in Eire.

A blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, N. Ireland, and Eire, the Ministry of Health and Local Government of N. Ireland, and the Department of Health of Eire.

CASES	1961 Eng. & Wales	1961 Lond.	1961 Scot.	1961 N. Ire.	1961 Eire	1960 Eng. & Wales	1960 Lond.	1960 Scot.	1960 N. Ire.	1960 Eire
Diphtheria	1	0	1	0		2	0	0	0	
Dysentery	313	33	110	5	2	448	54	109	11	
Encephalitis, acute	1	0		0		2	0	0	0	
Enteric fever:										
Typhoid	5	0	1	0		2	0	1	0	
Paratyphoid	4	0	1 (B)	0		7	3	0	0	
Food-poisoning	164	27	21	0		236	26	128	2	
Infective enteritis or diarrhoea under 2 years				23	20				21	
Measles*	8,154	145	48	88	118	2,545	147	35	0	
Meningococcal infection	24	2	5	1		12	1	16	1	
Ophthalmia neonatorum	14	0	3	0		18	3	2	0	
Pneumonia†	121	10	81	1	1	135	7	74	1	
Poliomyelitis, acute:										
Paralytic	14	1	2	1	3	4	1	0	0	
Non-paralytic	4	0				10	2	1		
Puerperal fever§	145	20	12	1		145	18	6	0	
Scarlet fever	268	24	14	12	14	316	19	30	9	
Tuberculosis:										
Respiratory	410	62	47	11		351	39	49	9	
Non-respiratory	64	6	9	2		45	7	11	1	
Whooping-cough	306	21	28	5	33	1,193	141	112	3	

DEATHS	1961 Eng. & Wales	1961 Lond.	1961 Scot.	1961 N. Ire.	1961 Eire	1960 Eng. & Wales	1960 Lond.	1960 Scot.	1960 N. Ire.	1960 Eire
Diphtheria	0	0	0	0	0	0	0	0	0	
Dysentery	0	0		0		0	0		0	
Encephalitis, acute		0			0		0			0
Enteric fever	0	0	0	0		0	0	0	0	
Infective enteritis or diarrhoea under 2 years	3	0	0	0	2	2	1	1	0	0
Influenza	1	0	0	0	0	1	0	0	0	0
Measles		0	0	0	1		0	0	0	0
Meningococcal infection		1	0				0	1		
Pneumonia	395	30	17	20	2	327	18	17	15	5
Poliomyelitis, acute	1	0		1	0	0	0		0	0
Scarlet fever		0	0	0	0		0	0	0	0
Tuberculosis:										
Respiratory	49	2	5	1	4	60	4	5	0	1
Non-respiratory		1		0	0		0	1	0	0
Whooping-cough	0	0	0	0	0	0	0	1	0	0
Deaths 0–1 year	312	33	31	4	12	290	32	29	6	9
Deaths (excluding stillbirths)	8,720	715	562	124	146	8,124	642	510	96	113
LIVE BIRTHS	16,214	1304	1037	280	427	14,085	1192	1070	229	358
STILLBIRTHS	299	24	23			280	17	31		

* Measles not notifiable in Scotland, whence returns are approximate.
† Includes primary and influenzal pneumonia.
§ Includes puerperal pyrexia.

Medical News

Rockefeller Foundation Grants

Rockefeller Foundation grants during the second quarter of 1961 totalled $8,736,292, of which $3,287,025 went to the medical and natural sciences. Among the grants was $28,000 to the National Board of Medical Examiners, Philadelphia, Pennsylvania, to develop a new examination for interns. This will attempt "to evaluate more accurately than present examining procedures the evasive, complex, and subtle aspects of clinical competence." In the United Kingdom grants were made to Dr. N. P. L. WILDY, assistant director of the Medical Research Council Unit for Experimental Virus Research, University of Glasgow, to observe recent developments in research on the ultrastructure of viruses at laboratories while in the United States and Canada, and to Dr. C. E. GORDON SMITH, senior lecturer in bacteriology at the London School of Hygiene and Tropical Medicine, to observe research at virus laboratories in the United States.

Chair in Clinical Bacteriology, Bristol University

Dr. W. A. GILLESPIE, lecturer in clinical bacteriology in the University of Bristol and consultant pathologist to the United Bristol Hospitals, has been appointed to the newly established, part-time chair in clinical bacteriology at that University.

Dr. Gillespie was educated at St. Andrew's College and Trinity College, Dublin, graduating M.B. in 1936. He was awarded the Adrian Stokes Memorial Fellowship in 1938. He obtained the M.R.C.P.I. and the D.P.H. in 1938 and proceeded M.D.(Dubl.) in 1942. He was elected Fellow of the Royal College of Physicians of Ireland in 1957. He held posts in the departments of pathology and bacteriology of the University of Dublin and was a clinical assistant in medicine at the Adelaide Hospital, Dublin. After a year in the Emergency Medical Service, he served from 1943 to 1947 as a pathologist in the Royal Army Medical Corps. He has held his present posts since then.

Damages for Paralysed Boy

Personal injury damages of $600,000 have been awarded to an 11-year-old boy in California who became paralysed after inoculation with Salk-type polio vaccine made by Cutter Laboratories, of Berkeley (*A.M.A. News*, July 24). In addition $75,000 was awarded to the boy's mother. An appeal has been entered against these decisions. The firm is reported to have already paid out $1,083,660 in response to other claims.

M.D.s and Osteopaths in U.S.A.

At the 110th annual meeting of the American Medical Association held recently in New York a long-standing ban against professional contact between doctors and osteopaths was ended when delegates passed a resolution agreeing that State medical associations should be allowed to decide whether such contact was ethical. Earlier in the year the California Medical Association, an affiliate of the A.M.A., had agreed that the two might co-operate because it believed that the A.M.A.'s policy of non-cooperation was "unrealistic," and furthermore had negotiated a merger between the State's physicians and osteopaths. The American Osteopathic Association's House of Delegates has voted to break off discussions with the A.M.A. "until such time as the A.M.A. demonstrates . . . that it is not their intent to destroy osteopathy." A.O.A. delegates also voted to increase the annual subscription to make up for the loss of its 1,500 Californian members, and to fight A.M.A. "encroachment." (*Medical Tribune*, July 24.)

U.S. Drug Firms Indicted

A New York grand jury has indicted three pharmaceutical firms and their chief executives under anti-trust laws on charges of fixing artificially high prices for, and monopolizing the production of, aureomycin, terramycin, and tetracycline. Those charged are Charles Pfizer Inc., and its president, J. E. McKeen; American Cyanamid Co., and its chairman, W. G. Malcolm; and Bristol-Myers Co., and F. N. Schwartz, its president.

Professional Classes Aid Council

Faced with the dilemma necessarily posed by insufficient funds—whether to give a lot to a few or a little to many—the Professional Classes Aid Council has embarked on what it describes as "for us an adventurous advertising campaign." Its *Fortieth Annual Report* shows that income amounted to £29,242 (compared with £24,217 last year), including £11,693 (£9,697) from subscriptions and donations, £3,869 (£3,508) from other organizations in connexion with almoner cases, and £10,346 (£9,812) from investments of the General Fund and the Annual Grant Funds. The total expenditure was £29,101 (£24,748), including £21,243 (£18,741) for relief. The figure for relief was made up of £3,895 for permanent help by annual grants, £10,311 for general relief by temporary help, £5,414 for education grants, and £1,623 for training grants. Of the 471 families given help, 164 were new, 22 were reapplications, and 285 were those needing continued help from one year to another; 452 applicants were not directly helped for various reasons. The Council's new address is 10 St. Christopher's Place, London W.1.

Western Provident Association for Hospital and Nursing Home Services

In its *Eleventh Annual Report, 1960*, the Western Provident Association for Hospital and Nursing Home Services, which started in 1945 as the British Hospitals Provident Fund, emphasizes that it operates on a national scale for consultant and specialist services. During the year the subscription income increased by £11,734, realizing a total figure of £193,565. Claims paid and outstanding totalled £155,519, an increase of £7,958 over the previous year. The claims ratio was 80% of the subscription income, compared with 81% in 1959 and 80% in 1958. Gross interest on investments reached £7,317, an increase of £1,964 over last year, and £3,571 was carried forward to the balance sheet, a figure which would have been substantially higher but for an increase in provision for unexpired risks. It is hoped to introduce a scheme in 1961 for helping subscribers with private general practitioners' fees. The W.P.A.'s address is 42 Baldwin Street, Bristol 1.

Colyer Prize

The Colyer Prize was founded in 1926 to commemorate the 25 years' service of Sir FRANK COLYER as honorary curator of the Odontological Museum. The accumulated income of this fund (about £20) is used every third year to award a prize for the best original work in dental science completed during the previous five years by a dental surgeon educated at any duly recognized dental school in Great Britain or Northern Ireland, and who has not been qualified to practise more than seven years at the date of the award. Applications from candidates, together with a general account of their researches, should be submitted to the Prize Committee, Colyer Prize, Royal Society of Medicine, 1 Wimpole Street, London W.1, by March 31, 1962, for consideration for the award due in July, 1962.

Hospital Building Bulletin

Accommodation for Nursing Staff is the title of the second Hospital Building Bulletin prepared by the Ministry of Health and the Department of Health for Scotland as part of their information service to help those who are concerned with the design and planning of hospitals. The Bulletins deal in a more detailed way with design and layout of selected hospital departments than do the Ministry's other series, Hospital Building Notes. Bulletin No. 2 costs 3s. net from H.M.S.O.

"Current Medical Research"

A reprint of the section "Some Aspects of Medical Research" from the *Report of the Medical Research Council for the Year 1959–1960* will be published in booklet form, under the title *Current Medical Research*, on September 22. (H.M.S.O., price 4s., by post 4s. 5d.)

"Journal of Sport Medicine and Physical Fitness"

The new quarterly *Journal of Sport Medicine and Physical Fitness* is the official journal of the Fédération Internationale de Médecine Sportive, and is published in English with summaries in French, German, and Italian. The yearly subscription is £2 16s. 4d. ($8), and inquiries should be sent to the publishers, Minerva Medica, 83–85 Corso Bramante, Turin, Italy.

In Brief

▶ The United Kingdom will contribute £25,000 to the cost of the new multi-racial hospital at Salisbury, Southern Rhodesia, which will be the teaching hospital for the medical school to be established at the University College of Rhodesia and Nyasaland.

▶ On August 16 the PRINCESS ROYAL opened a new £125,000 out-patient and casualty block at the Skipton General Hospital which she opened nearly 30 years ago. The new block houses, in addition, radiology, pharmaceutical, and physiotherapy departments, pathological laboratories, a chest clinic, and accommodation for almoners and health visitors.

People in the News

▶ Surgeon Rear-Admiral (D.) W. HOLGATE has been appointed Chief Dental Officer, Ministry of Health, from December 1 in succession to DR. W. G. SENIOR, who is retiring.

▶ Dr. B. S. ROSE, medical superintendent, Queen Elizabeth Hospital, Rotorua, New Zealand, and formerly senior registrar and tutor in the department of child health and paediatrics, University of Leeds, has been awarded a W.H.O. Fellowship to study developments in rheumatology overseas.

▶ Professor MARIO D'ALMEIDA, of Rio de Janeiro, who holds the only chair of anaesthetics in South America, has been created a C.B.E. Professor d'Almeida did postgraduate work in the departments of anaesthetics at the London Hospital and at Oxford, and was the first South American to be awarded the F.F.A. of the Royal College of Surgeons. He has for long been on the staff of the Strangers Hospital in Rio de Janeiro, and during the war years and since has done valuable work for the British community in that city.

COMING EVENTS

Universities Federation for Animal Welfare.—Broadcast appeal by Mr. Sydney Jennings (President of the British Veterinary Association), B.B.C. Home Service, August 27, 8.25 p.m.

5th International Pigment Cell Conference.—Sponsored by New York Academy of Sciences, October 11–14, New York City, and dealing with melanoma and closely related fields. Details from Dr. V. RILEY and Dr. J. G. FORTNER, Sloan-Kettering Institute for Cancer Research, New York 21, N.Y., U.S.A.

British Diabetic Association.—Autumn meeting of medical and scientific section, September 29, 30. Chairmen: Professor J. R. SQUIRE, Dr. J. M. MALINS, Professor F. G. YOUNG, F.R.S. Details from Dr. D. A. PYKE, King's College Hospital, London S.E.5.

2nd International Congress of Neurological Surgery.—Organized and conducted by World Federation of Neurosurgical Societies, Washington, D.C., October 14–20. Details from Dr. BRONSON S. RAY, Secretary-General, 525 E. 68th Street, New York 21, N.Y., U.S.A.

NEW ISSUES OF SPECIALIST JOURNALS

The journals listed below are obtainable from the Publishing Manager, B.M.A. House, Tavistock Square, London W.C.1.

ARCHIVES OF DISEASE IN CHILDHOOD

Hypoplastic Anaemia in Infancy and Childhood: Erythroid Hypoplasia. D. W. O'Gorman Hughes.
Red Cell Cholinesterase in Infancy and Childhood. David Burman.
Primary Myocardial Disease in Infancy: Clinical Aspects. John Apley.
Hypervitaminosis D with Osteosclerosis. Loren T. DeWind.
Systematic Ventriculographic Studies in Infants Born with Meningomyelocele and Encephalocele: The Incidence and Development of Hydrocephalus. John Lorber.
Accidental Poisoning in Children. M. A. Heasman.
Bowel Infection and Acute Appendicitis. M. E. E. White, M. D. Lord, and K. B. Rogers.
A New Technique in Exchange Transfusion. Trevor Wright.
Congenital Abnormalities in the African Newborn. Michael Simpkiss and Anne Lowe.
Delayed Visual Maturation. R. S. Illingworth.
Congenital Abnormalities of the Femur. P. A. Ring.
Hydramnios in Relation to Foetal Mortality. K. A. Rahimtulla.
Cleft Lip and Palate: Seasonal Incidence, Birth Weight, Birth Rank, Sex, Site, Associated Malformations and Parental Age: A Statistical Survey. G. R. Fraser and J. S. Calnan.
Leukaemic Meningitis. D. G. Cottom and G. Wetherley-Mein.
Lipodystrophic Muscular Hypertrophy. B. Senior.
Three Differing Cases of Glycogen Storage Disease. D. G. Walker, M. Zial, and J. E. Bowman.
A Case of Precocious Puberty in a Female. Murray McGeorge and D. V. Connor.
The Postnatal Development of Alveoli in Premature Infants. Avinash Mithal and John L. Emery.
Vomiting in the Early Days of Life. W. S. Craig.
Book Reviews.

Volume 36, No. 188. (Bi-monthly; £4 4s.)

SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ●. Application should be made first to the institution concerned.

Friday, September 1

INSTITUTE OF DISEASES OF THE CHEST.—5 p.m., Dr. J. R. Bignall: clinical demonstration.

EAST ANGLIAN REGIONAL HOSPITAL BOARD.—J. P. N. Hicks, M.B., B.S., F.F.A. R.C.S., Consultant Anaesthetist, Norwich, Lowestoft and Great Yarmouth Hospital Group; C. Q. Henriques, M.Chir., F.R.C.S., Consultant Surgeon, Ipswich and East Suffolk Hospital Group; O. Sunar, M.D., Ear, Nose, and Throat Registrar, Norfolk and Norwich Hospital and Jenny Lind Children's Hospital, Norwich. D. Keith, L.R.C.P.&S.Ed., Ophthalmic Registrar, Ipswich and East Suffolk Hospital; G. E. Dimopoulos, M.B., B.Ch., Surgical Registrar, and S. N. Prasad, M.B., B.S., Surgical Registrar (Casualty), Peterborough Memorial Hospital.

LONDON TRANSPORT.—James Fairlee, B.Pharm., M.R.C.S., L.R.C.P., D.I.H., and G. C. Acres, M.R.C.S., L.R.C.P., D.I.H., Officers of London Transport Executive from July 1, 1961.

NORTH-WEST METROPOLITAN REGIONAL HOSPITAL BOARD.—Agnes M. Main, M.B., B.S., Consultant Child Psychiatrist, Twickenham Child Guidance Clinic and Staines Child Guidance Clinic; P. W. D. Corfield, M.S., F.R.C.S., Consultant General Surgeon, Wembley Hospital.

BIRTHS, MARRIAGES, AND DEATHS

BIRTHS

Hooper.—On August 13, 1961, at Princess Mary's R.A.F. Hospital, Halton, Bucks, to Howys (formerly Spencer-Lloyd) and Dr. William L. Hooper, a daughter—Anne.

Jamieson.—On July 20, 1961, at Queen Elizabeth Maternity Unit, King's Lynn General Hospital, Norfolk, to Pamela and Ian W. Jamieson, M.B., Ch.B., a son—Andrew Ewen.

Phear.—On August 12, 1961, at Queen Elizabeth Hospital, Adelaide, South Australia, to Margaret, wife of Dr. David N. Phear, a brother for Philippa—Alan Graham.

DEATHS

Aspinall.—On July 17, 1961, as the result of an accident on the Aden Peninsula, Alfred Aspinall, M.B., Ch.B., Lieutenant, R.A.M.C., aged 27.

Belcher.—On August 1, 1961, in London, Ormonde Rashleigh Belcher, L.R.C.P.&S.Ed., L.R.F.P.S., formerly of 137 Queen's Drive, Liverpool, aged 78.

Brandon.—On July 27, 1961, at Carlton Cottage, Pyrford, Surrey, Gordon Normanby Brandon, F.R.C.S.

Fellowes.—On July 19, 1961, Vera Fellowes, M.B., Ch.B., of 20 Mackenzie Road, Moseley, Birmingham.

Hills.—On July 21, 1961, at 38 Woodside House, Wimbledon, London S.W., William Charles Dillon Hills, M.R.C.S., L.R.C.P., D.P.H., aged 90.

Holmes.—On July 24, 1961, at Llandough Hospital, Cardiff, David Price Holmes, T.D., M.D. D.P.H., Colonel, R.A.M.C., A.E.R.

Kelleher.—On August 3, 1961, at 44 Queens Park Road, Blackburn, Lancs, Dermot Kelleher, M.B., B.Ch., aged 64.

Marshall.—On July 21, 1961, at Royal Victoria Hospital, Belfast, James Lister Marshall, M.B., B.Ch., of Pembroke House, Markethill, Co. Armagh.

Smith.—On July 21, 1961, at Birmingham, Warwicks, David Priestley Smith, M.B., Ch.B., of 80 Oakham Road, Harborne, Birmingham, aged 77.

Talboys.—On July 20, 1961, at St. Bartholomew's Hospital, London E.C., Kenneth Talboys, L.M.S.S.A.

Any Questions?

We publish below a selection of those questions and answers which seem of general interest. It is regretted that it is not possible to supply answers to all questions submitted.

Immunization of Poliomyelitis Contacts

Q.—*Is immunization with inactivated vaccine of a poliomyelitis contact contraindicated? Is there a risk of provocation poliomyelitis?*

A.—There are two opposing views on the immunization of contacts of a case of poliomyelitis. The first is that the procedure is to be recommended and should be combined with some form of house-quarantine. However, the second, contrary view is that such an immunological procedure is of no practical value because the contacts of a clinical case are probably already infected; antibody production has been stimulated by the infection and cannot be increased rapidly by the injection of more antigen.

The question of "provocation" polio does not arise. Authorities are now more or less agreed that inoculations of polio vaccine do not light up a latent infection nor cause a fresh one.

There is much to be said for the view that when a case of clinical polio makes its appearance the non-immune people at the periphery rather than the close contacts of the patient should be immunized as quickly as possible.

Sleep in the Antarctic

Q.—*Can the prevalence of insomnia in a small, closed community, such as an Antarctic base, be taken as an index of mental strain?*

A.—Sleep requirements in polar regions have been studied by Lewis and Masterton,[1] who found that, although the pattern of sleeping varied widely in many individuals, the average amount of sleep taken during the 24 hours was eight hours. The sleep pattern varied from cat-naps to continuous sleep of eight hours' duration. Non-psychic factors affecting sleep rhythms in polar regions may be altered relationships between body diurnal rhythms and local time associated with change of longitude and effects of continuous daylight during the summer months. In any case, it would seem very unlikely that insomnia under these conditions should be taken as an index of mental strain.

REFERENCE

[1] Lewis, H. E., and Masterton, J. P., *Lancet*, 1957, **1**, 1262.

Cilia-paralysing Drugs

Q.—*What drugs paralyse the cilia of ciliated epithelium?*

A.—The cilia of ciliated epithelium beat rhythmically, producing a wave-like effect which washes material on the surface of the epithelium towards the appropriate orifice. This rhythmic activity is independent of nervous control and continues for several hours after the death of the organism. Among the factors which influence the rhythmic activity the most important are local conditions, such as temperature, and the composition and viscosity of the fluid bathing the surface of the ciliated epithelium. The rhythm is slowed by cold and quickened by warmth, but heat a few degrees above the temperature of the organism will stop ciliary activity. The *p*H of the fluid is important; Negus[1] found that at *p*H 8.5 ciliary activity was extremely vigorous but that dilute acid solutions slowed the rhythm, and at *p*H 6.4 or less the cilia were paralysed. The presence of calcium is essential for ciliary activity and the concentration of other cations such as sodium, potassium, and magnesium will influence the rhythm. Of extrinsic substances which are known to affect ciliary movement, general anaesthetics and sedatives depress and may temporarily paralyse the cilia, so also does tobacco smoke and small doses of *x*-radiation. The influence of local applications which are commonly applied to the ciliated epithelium of the nose is variable; chlorbutol, 0.5% solution, paralyses, glycerin has a retarding action, but silver protein salts have no effect.[1] The action of cilia is uninfluenced by many powerful pharmacological substances including adrenaline, acetylcholine, and histamine.

REFERENCE

[1] Negus, V. E., *J. Laryng.*, 1934, **49**, 571.

Tonsillectomy in the Summer

Q.—*What is the present general policy in performing tonsillectomy in children during the summer months, even in those children who have had adequate doses of Salk-type vaccine?*

A.—It is customary to continue with the operation for tonsillectomy during the summer months provided that there is no local incidence of poliomyelitis in the area in which the hospital is situated or the patient is resident. The local medical officer of health will usually notify all the doctors in his area of the occurrence of any cases of polio and will often recommend that operations should be postponed during an epidemic. Furthermore, it is now usual to record on the hospital admission slip whether a patient, especially a child or a young adult, has been protected by a vaccine, and, if so, how many injections have been given.

Skin Testing for Allergy

Q.—*Is skin sensitivity testing in cases of asthma, allergic rhinitis, etc., of any value in diagnosis or as a guide to treatment?*

A.—Skin testing is of value when investigating possible allergic causes of asthma, allergic rhinitis, etc. However, the interpretation of the results of positive and even negative skin tests is not always easy, and may require much experience. A positive skin test always means something, but it may mean nothing more than the fact that an irritating substance was introduced into the skin, possibly traumatically, and that someone read the result as positive. The methods of reading the results and the extracts used have not been standardized. Moreover, skin tests are not quantitative, so that a large positive skin test does not mean that the patient is very sensitive, although unfortunately this is what is so often reported. The history will usually indicate how sensitive a patient is, and the main use of skin tests is to confirm a carefully taken history. Allergic rhinitis which is non-seasonal and non-environmental is probably not "allergic," and one would expect that skin tests in such a condition would be negative. If the basic immunological problems involved in an allergic reaction are understood, and if it is realized that with impure, non-standardized extracts there are great limitations in interpretation, much useful information and, particularly, confirmation of the clinical history can be obtained from an investigation such as skin testing.

Eggs for Small Boys

Q.—*In view of the present awareness of a possible unfavourable effect of dietary fat of animal origin, would it be unwise to give small boys a daily egg with its high cholesterol content?*

A.—The part played by a high dietary intake of animal fat in the production of occlusive artery disease is not sufficiently understood for it to be suggested that eggs should be removed from the diet of small boys. Many factors are concerned in the production of this type of arterial disease, and there is as yet no proof that restricting the intake of cholesterol will prevent or reverse the disease in a given individual, although population and other studies suggest that a high intake of saturated animal fat is associated with a high incidence of arterial disease.

The only reason for restricting the intake of eggs and other foods containing cholesterol in small boys would be hypercholesterolaemia or a strong family history of premature occlusive artery disease.

Hypnotherapy for Refractive Errors

Q.—*I have recently been requested to give an opinion on the possibilities of hypnotherapy in the treatment of errors of refraction. I should appreciate your views.*

A.—Any patient *completely* under the spell of a hypnotist might be relieved from symptoms, even if he were the victim of a perforated duodenal ulcer. In the same limited sense we can agree that symptoms arising from refractive errors can be suspended by hypnosis. Hypnosis would not, however, change the refraction, and it is not a reputable method of treatment for optical defects.

Adrenochrome Monosemicarbazone in Dental Haemorrhage

Q.—*What is the value of "adrenoxyl" (adrenochrome monosemicarbazone) in preventing dental haemorrhage?*

A.—Several articles have been published by clinicians attributing haemostatic properties to adrenoxyl in dental surgery. Double blind experiments on patients and animal experiments have failed, however, to substantiate this, and indicate that it is probably of no value.

Purple Ring with Benedict's Test

Q.—*Sometimes with Benedict's test for glycosuria a very dark purple ring is formed at the surface of the solution while it is still cold. In such cases the solution has usually gone turbid and green when boiled, from which I have presumed that a small amount of sugar is present. What is the significance of the purple ring?*

A.—These colour reactions can be produced by a variety of chemical substances, and it is important to know the reaction of the urine in the cases referred to. If, as is likely, the urine was alkaline, then the most probable cause is proteinuria, which would account both for the purple ring and for the green turbidity on boiling.

Fat Balance in Fat Malabsorption in Children

Q.—*For estimating whether steatorrhoea is present in an adult the usual screening test employed in the first instance is that on an average diet of 50 to 150 g. of fat per day total faecal fat of more than 7 g. indicates malabsorption. What is the generally accepted way to assess a similar patient in the age-group birth to 5 years, especially in a case where milk products constitute most of the diet? If one can assess the total fat intake, is there a threshold above which the ratio of fat intake to faecal fat should not normally rise, and are estimations of the ratio of split to unsplit fat of any value? I am thinking particularly of cases in the first year of life in which the question of mild fibrocystic disease of the pancreas arises, and when simple analysis of duodenal juice suggests that tryptic activity is normal.*

A.—Different experts tend to hold different ideas on the best way of carrying out a fat balance on a child, but in general a balance of three to five days in which over 90% of the dietary fat is absorbed may be considered normal. The absorption in an adult is nearer 95%, but in smaller children and infants anything above 90% is probably acceptable as being within the normal limit. Certainly a total faecal fat excretion in any single day is of no value in indicating the possibility of malabsorption, and any method short of a detailed fat balance can lead to serious error. Estimations of the ratio of split to unsplit fat are of little value, and from the practical and diagnostic point of view of no value. A few people, after much experience, are able to give a very good appraisal of the possibilities of steatorrhoea by microscopic examination of the stools when there is a marked excess of fat globules or of undigested muscle fibres, but this test, in the absence of a very experienced expert, is also liable to lead to misdiagnosis.

Simple analysis of the duodenal juice, if an alkaline and yellow juice has been obtained, is a very reliable test in the diagnosis of cystic fibrosis of the pancreas, and if the tryptic activity under those conditions is normal the diagnosis of this condition has been almost excluded. A further test of simplicity is the finger sweat test, and if a further confirmation of the diagnosis is needed a complete sweat test with analysis of the content of sodium and chloride of the sweat is advisable.

Qualified Privilege of Medical Records

Q.—*A patient confided in the course of a normal medical examination and history taking that he was a homosexual. Might an entry of this important information on his N.H.S. medical record card possibly lead to legal proceedings against the patient or to an action for libel against the doctor?*

A.—It would be quite in order for a doctor to enter on a patient's record card that the patient "says he is a homosexual." The mere fact that the patient admits that he is a homosexual does not in itself indicate that he has committed a criminal offence. In any event, an entry recorded by a doctor on a patient's record card is covered by qualified privilege and would not be actionable unless it could be shown that the statement was actuated by malice.

NOTES AND COMMENTS

Nettle-sting for Rheumatism.—Mr. J. R. M. WHIGHAM (London S.W.1) writes: An acquaintance of mine went with his wife to France very recently on a hard-earned holiday. On the first day she developed what she described as "excruciating lumbago." She very reluctantly decided to return home. When the hotel proprietor was told of this he asked if he might be permitted to treat her. This he did by applying nettles as mentioned by your questioner ("Any Questions?" July 29, p. 323). The result—immediate and complete relief. Floreat grandmamma!

Corrections.—In Table I of the paper on methoserpidine by Dr. Mary Holt (August 12, p. 415), the word "failure" should have appeared instead of the word "fair" in the column headed "Response." In Table IV, the final entry in the last column—"Sense of unreality, 1, Nausea, 1"—applies to Read's series and not to the present series. In the second line of the final paragraph of the discussion, the word hypertensive was printed instead of hypotensive.

In our report of the address commemorating the centenary of the birth of Sir Almroth Wright (*Journal*, August 19, p. 516) we wrongly described the speaker, Brigadier L. R. S. MacFarlane, as professor of pathology at the Royal Army Medical College, Millbank. Brigadier MacFarlane no longer holds this chair, being now director of pathology at the War Office. The present professor of pathology at the Royal Army Medical College is Colonel H. C. Jeffrey.

The price of "skefron" is 8s. 6d. for a 5 fl. oz. container, not 10s. 5d. as shown in "To-day's Drugs" (August 12, p. 451).

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